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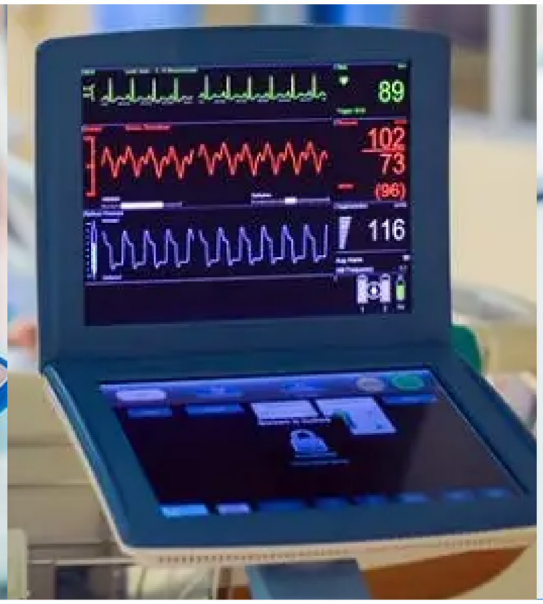

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ORIGINAL ARTICLE

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LETTER TO THE EDITOR

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Original Article

Determining the clarithromycin-resistance of *Helicobacter pylori* in first-line therapy with melting curve analysis

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ABSTRACT

Aims: We aimed to determine the usefulness of melting curve analysis with the PCR technique in predicting the primary clarithromycin resistance of *H. pylori* before antibiotic use.

Methods: 46 *H. pylori* positive clarithromycin based therapy naïve patients were included in the study. After proving *H. pylori* positivity with a real-time test, histopathological examination and rapid urease test, patients were treated with clarithromycin-based triple therapy for 14 days. Then patients were underwent a control endoscopy and tissue samples were taken 8 weeks after the initial endoscopy. The presence of *H. pylori* was investigated by using TaqMan-based real-time PCR and clarithromycin resistance was determined using two different molecular methods:melting curve analysis and DNA sequencing.

Results: In total 18 patients (39.1%) were diagnosed as *H. pylori* positive on histopathological examination and 26 (56.5%) were diagnosed as *H. pylori* positive with TaqMan-based PCR, after triple therapy. According to results of melting curve analysis, primary resistance was found in 4 samples before treatment and secondary resistance was found in a different 4 samples after treatment. The DNA analysis showed that 9 patients had primary mutations in the pre-treatment group:4 patients had A2142C-A2143G(T), 3 patients had T2182C, and 2 patients had both mutations, and also showed that 6 patients had mutations in the post-treatment group:4 patients had A2142C-A2143G, 2 patients had T2182C mutations.

Conclusion: PCR based melting curve analysis may fail in determining clarithromycin resistance before eradication therapy. Hence, this method may also be used in combination with another molecular method such as DNA sequence analysis for improved detection of clarithromycin resistance.

Keywords: *Helicobacter pylori*, clarithromycin resistance, triple therapy, melting curve analysis

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is the most common gastrointestinal system related bacterial infection throughout the world, and has been suggested to cause gastritis, peptic ulcer disease, and gastric cancer. Clarithromycin based triple therapy is still the first line treatment for *H. pylori* infection, although reported evidence suggests high rates of resistance and, primary and acquired clarithromycin resistance is increasing worldwide.[1-3] Some common reasons for increased drug resistance are past medical history of previous clarithromycin usage and noncompliance to triple treatment. Although clarithromycin plays a key role in the treatment of *H. pylori*, increasing drug resistance has resulted in a failure of complete eradication of the bacteria.[4] Clarithromycin resistance has been reported to be 5%-10% in the USA, 1%-8% in Europe and changing heterogeneously from 11.4% to over 56% in Turkey according to results of previously published studies.[4-6]

In countries where the prevalence of clarithromycin resistance is high, determining the susceptibility of *H. pylori* against clarithromycin is so important before initiating an eradication regimen. Resistance to clarithromycin is a result of point mutations within the peptidyltransferase-encoding region of the 23S rRNA gene.[7] Three major point mutations in two positions on the 23S rRNA have been described: A2142C, A2142G, and A2143G.[7-10] A2142G and A2143G are the most frequently seen mutations, whereas mutation A2142C is less common. Point mutations at A2115G and G2141A have been shown to occur in the same strain.[9-11] Histopathology[12], *H. pylori* cell culture[13,14] and Fluorescence in Situ Hybridization (FISH)[15,16] are some of the current methods that are used for determining clarithromycin susceptibility. Several PCR-based techniques have been developed to determine these 23S rRNA related mutations.[11,17] A real-time PCR method which is based on amplification of a fragment of the 23S rRNA gene of *H. pylori* followed by melting curve analysis was also developed and used firstly by Gibson et al. on *H. pylori* strains.[18]

In this study, we aimed to determine the usefulness of melting curve analysis with the PCR technique in predicting the primary clarithromycin resistance of *H. pylori* before antibiotic use in patients with confirmed *H. pylori* infection.

METHODS

Ethics

The study was carried out as thesis study in 2008. All ethical procedures and standards were carried out in accordance with the 1975 Helsinki Declaration.

Study Group and Sample Collection

The study was conducted at the Gulhane Military Medical Academy, Gastroenterology outpatient clinic, as a thesis study in year 2008, in Ankara, Turkey. A total of 46 *H. pylori* positive patients admitted to the gastroenterology outpatient clinic with chronic dyspeptic symptoms and who had not been treated with clarithromycin were included in the study. The presence of at least three of six symptoms (epigastric pain, heartburn, nausea, gas, bloating and belch) with a duration of not less than 4 weeks was established as the inclusion criteria for the study. Patients younger than 18 years or older than 65 years, those previously treated for *H. pylori* infection, those with a medical history of cholelithiasis, bleeding diasthesis, chronic disease or duodenum related surgery, drug history of non-steroidal anti-inflammatory drugs (NSAIDs) three months prior to endoscopy or erythromycin usage for any other reason were excluded from the study.

The gastric biopsy specimens were obtained from all patients during upper gastroduodenal endoscopy. A total of six biopsy specimens, including two specimens each from the antrum, and greater and smaller curvatures of the stomach, were obtained from all participants. For the Rapid Urease Test (Clo test), a biopsy specimen was obtained from the antrum and a specimen each from the antrum and greater curvature was obtained for the clarithromycin susceptibility studies. Patients with histopathologically confirmed diagnosis of *H. pylori* and a positive urease test were prescribed lansoprazole 30 mg capsule, amoxicillin 1000 mg tablet and clarithromycin 500 mg tablet all twice daily for 14 days. A control endoscopy was performed on all patients and biopsy samples were obtained again 8 weeks after the initial endoscopy.

Histopathological Examination

Biopsy specimens were put into sterilized containers, which included formaldehyde (10.0%), and transported to the pathology laboratory. All samples were embedded in paraffin. The paraffin-embedded tissue sections were stained using toluidine blue and hematoxylin and eosin, and examined with a light-microscope for the presence of *H. pylori* and other morphological findings.

DNA Extraction

For the clarithromycin susceptibility studies, collected biopsy specimens were stored at -20°C in Eppendorf tubes with 1ml 0.9% NaCl solution. Template DNA was extracted from biopsy specimens using the standard phenol-chloroform-isoamyl alcohol method.19 Briefly, approximately 40 mg of tissue samples were minced and suspended in 500 µl of TE buffer (10 mM Trishydrochloride, 1 mM EDTA, pH 8), and homogenized by vigorous mixing on a vortex. A 10 µl aliquot of protease solution (65 mg/ml) (Sigma-Aldrich Corp, St. Louis, MO, USA) and 250 µl of K buffer were added to the 250 µl of mixed specimen and incubated for 60 min at 45°C. Following centrifugation at 10,000 g for 10 min at 12°C, DNA was extracted from the supernatant using a mixture of 250 µl alkali phenol and 250 µl chloroform-isoamyl alcohol (24:1), and then precipitated using 500 µl isopropyl alcohol. The DNA was washed in 75% ethyl alcohol, centrifuged at 10,000 g for 5 min at 4°C, air-dried at 37°C and dissolved in 100 µl distilled water.

Real Time PCR Analyses

TaqMan based real-time PCR assays were used for the detection of *H. pylori* in biopsy specimens. The primers and probes used in this study are shown in **Table 1**. The reaction mixture was prepared for all real-time PCR assays as follows: 1.25 U Hot Start Taq DNA polymerase (Bioron, Germany), 10 pmol of each primer, 2.5 pmol TaqMan probe, 0.2 mM dNTP mix, and 2.5 mM $MgCl_2$. PCR amplifications were carried out in a final volume of 25 µL of the PCR reaction mixture, after the addition of 5 µl of the sample containing template DNA. The amplification conditions were as follows: Initial denaturation for 10 min at 95°C, followed by 40 amplification cycles of 15 s each at 95°C and 1 min at 60°C (annealing-extension step).[20] The primers and probes were designed using the OligoYap 4.0 software program.[21] All primer and probe sequences were analyzed with the GenBank BLAST database for specificity, and were synthesized by MWG-Biotech (Ebersberg, Germany). The TaqMan probes were labeled with a fluorescent reporter dye (FAM: 6-carboxy fluorescein) at the 5' end, and with black hole quencher (BHQ) as the non-fluorescent quencher at the 3' end. The human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene was used as an internal control,[22] and the PCR mixture without the template DNA was used as a negative control. Bacterial isolates used as a positive control originated from the strains of our laboratory. The *H. pylori*-specific amplicons and the GAPDH amplicon were cloned into plasmid vectors using a TOPO TA Cloning System (Invitrogen, USA). Serial plasmid dilutions (108-101 copies/ml) were prepared for determining the detection sensitivities of the PCR assays. The calculation of standards was performed using spectrophotometry and OligoYap 4.0 software. All PCR analyses were performed using an iCycler thermal cycler instrument (Bio-Rad, USA).

Table 1. Primers and probes used in real-time PCR assays

Target genes		Primers and probes	Amplicon size
H. pylori	23S rRNA gene	F: 5'-agcattgtcctgcctgtggataa-3' R: 5'-ggttaaataccgacctgcatgaat-3' P (antisense): 5'-FAM-acctttactacaacttagcactgctaat-BHQ-3'	285 bp
Internal control (GAPDH)	Human GAPDH gene	P1: 5'-tcctgcaccaccaactgcttag-3' P2 : 5'- catcacrccacagyttyccagag-3' Probe: 5'-FAM-aggtcatccatgacaactttggyatcg-BHQ -3'	145 bp

Abbreviations: F: forward primer, R: reverse primer, and P: probe.*R and Y codes indicate degenerate bases; R=(A/G), and Y=(C/T). bp (base pairs).

Melting Curve Analysis

SYBR Green-based PCR reactions were performed for melting curve analysis using the same primers that were used in the TaqMan-based type-specific real-time PCR (**Table 1**). PCR reactions were carried out in a total of 25 µl volumes containing 10 pmol of each primer, a final concentration of 1X SYBR Green I, 0.25 mM dNTPs, 2.0 mM $MgCl_2$, and template DNA. PCR amplification cycles were as follows: a single cycle for 10 min at 95°C (hot-start Taq DNA polymerase activation), followed by 40 amplification cycles of 15 sec each at 95°C and 1 min at 60°C (annealing-extension step). After completion of the 40 PCR cycles, the melting-curve data were obtained by continuous fluorescence acquisition from 55 to 95°C, with a thermal transition rate of 0.1 °C/s.[22]

DNA Sequencing

PCR amplicons were obtained in our laboratory by using the sense and antisense primers from biopsy specimens that revealed the presence of bacteria before and after treatment, and sent to the MWS Company (Germany) for DNA sequencing. A total of 58 *H. pylori* positive samples (39 obtained before treatment and 19 samples obtained from the post-treatment group) were sequenced, while other samples were evaluated that were not suitable for sequence analysis.

Statistical Analysis

The Chi-square test was used to evaluate the statistical significance of the difference between groups, and p values <0.05 were considered significant (at the 95% confidence interval). Statistical analyses were conducted using the Statistical Package for the Social Sciences (SSPS) 15.0 software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Of the 46 patients, 14 (30.4%) were males and 32 (69.6%) were females. The mean age of the patients was 37.05 ±11.57. When pre-treatment and post-treatment findings were compared among patients, the relationships among response rate, age, gender, endoscopic findings, treatment response, smoking and mutant genes did not show any significant differences.

Histopathological findings revealed that *H. pylori* positivity was present in 46 (100%) patients before treatment and in 18 (39.1%) patients after treatment. The PCR technique detected *H. pylori* positivity in 46 (100%) patients before treatment and in 26 (56.5%) patients after treatment. By using the TaqMan PCR, the analysis we conducted showed positivity for *H. pylori* in all of the 46 collected biopsy specimens before treatment and positivity in 26 biopsy specimens after treatment. As a result of our SYBR Green I and Melting Curve Analysis study, we detected primary resistance in 4 biopsy samples collected before treatment and secondary resistance in a different 4 biopsy specimens after treatment.

DNA sequencing analysis of *H. pylori* strains was successfully accomplished in 39 patients before treatment and 19 patients after treatment. All other samples were not found to be suitable for sequencing analysis. DNA sequence analysis detected resistant strains in 15 patients (34.8%) from both groups: 9 of these patients had primary mutations in the pre-treatment group, and 6 patients had mutations in the post-treatment group. The mutations found in the post-treatment group were not part of the pre-treatment primary resistance but rather developed during treatment. Results from DNA sequencing analysis in both pre treatment and post treatment groups are shown in **Table 2**.

Table 2. Patients have clarithromycin resistant *H. pylori* strains before and after treatment

	Mutation types	Number of patients
Pre treatment (39 patients)	A2142C-2143G(T)	4 (10.26%)
	T2182C	3 (7.69%)
	Concurrent (double) mutations; A2142-C2143G(T) and T2182C.	2 (5.13%)
	Total	9 (23.08%)
Post treatment (19 patients)	A2142C-2143G(T)	4 (% 21.05)
	T2182C	2 (10.52%)
	Concurrent (double) mutations	0
	Total	6 (%31.57)

Graphics of the Melting Curve analysis are shown in **Figure 1**, **Figure 2** and **Figure 3**.

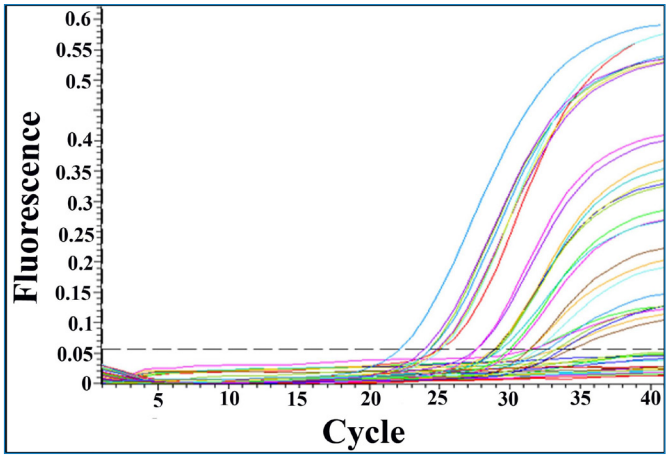

Figure 1. TaqMAN real time PCR peaks of *H. pylori* positive and negative samples. The peaks under dotted line are negative peaks

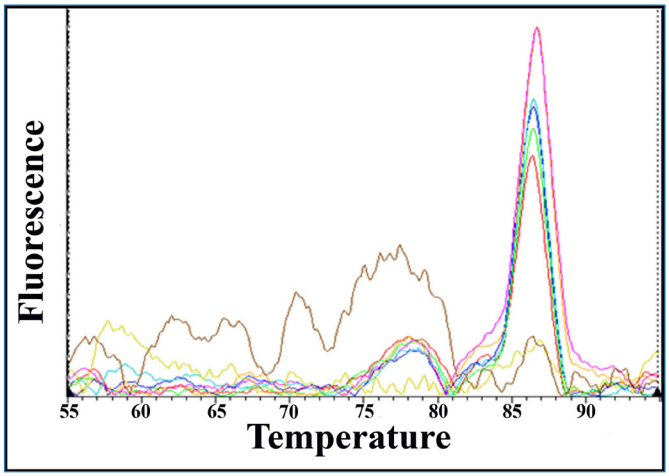

Figure 2. Melting curve graphic of *H. pylori* positive and irresistant samples between 86.2–86.9°C

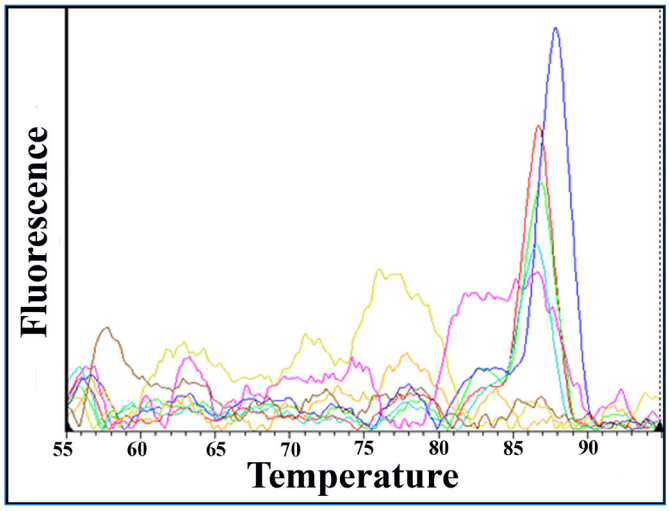

Figure 3. Melting curve graphic of *H. pylori* positive and resistant/ irresistant samples between 86.5–87.1°C. Blue peak is at 87.1°C and different from normal appearing.

DISCUSSION

Clarithromycin resistance to *H. pylori* occurs as a result of single-base mutations within the peptidyltransferase-encoding region of the 23S rRNA gene. The most commonly encountered mutations are A2142G, A2143G, A2144G, C2182T, and with a lower incidence A2143C. Other rarely seen mutations are G2141A, A2143T, T2183C, T2245C, A2144T and T2717C. Distribution of these mutations show regional differences.[7-11]

In previous research, Chen et al. demonstrated A2143G mutation in 11.11% and C2182T mutation in 12.96 % of 54 patients before treatment, via DNA sequencing using the PCR technique. This was later confirmed by DNA sequencing analysis.[23] In Chile, Garrido et al.[24] studied 50 patients with no history of clarithromycin exposure and found primary resistance in 10 (20%) of the patients, using the agar dilution method. Point mutations were observed in four of the ten patients and two or more mutations were observed in other six cases. In 9 patients, A2142G mutation was seen and A2143G mutation was observed in only one patient. Other detected mutations from the isolates were C2147G, G1939A, T1942C and A2142G. Similar mutations were seen after nucleotide sequencing. In our study, out of the 39 patients who were considered appropriate for DNA analysis, we found primary resistance in 4 (10.26%) patients with A2142C-2143G(T) mutations, in 3 (7.69%) patients with T2182C mutation, and in 2 (5.13%) patients with both mutations. We found the total mutant gene ratio to be 23.08%. This result was similar to the resistance ratio (20%) of Garrido et al.'s study.[24] Of the 9 patients, in whom primary resistance was detected prior to treatment, complete eradication of *H. pylori* failed in 3 patients and the remaining 6 patients exhibited absence of *H. pylori* after treatment. Among the 19 patients, in whom DNA sequencing analysis was performed after treatment, we found A2142-2143G mutations in 21.05% (4/19) of patients and T2182C mutation in 10.52% (2/19) of patients. These mutations were not a part of pre-treatment primary resistance, but rather developed during treatment. Following treatment, A2142-2143G and T2182C point mutations were seen to be absent in resistant strains. The mutant gene ratio found in our study is closer that in the results from Chen et al.'s[23] study, which was conducted in China.

In another *H. pylori* study, 470 patients were enrolled by Mahachai et al.[25] the eradication rate was 90.6% in clarithromycin sensitive patients compared to an eradication rate of 56.3% in clarithromycin resistant patients. Also in a similar study conducted by Vincenzo et al.[26] 75 patients with *H. pylori* were given PPI, amoxicillin and clarithromycin for seven days. Upon further evaluation, eradication was achieved in 11(48%) of the 23 patients who showed A2143G mutation-associated clarithromycin resistance and 14 (93%) patients with resistance due to either A2142G or A2142C mutations.

Of the six patients in whom we detected secondary resistance, histopathological findings revealed failure of *H. pylori* eradication in four patients. However, two patients were completely eradicated. Among the patients with secondary resistance, we found an eradication rate of 33.34%. In the paper by Chen et al.[27] while *H. pylori* positivity was found in all patients via PCR, histopathological evaluation revealed two-thirds of the patients to be positive. The difference in results was attributed to the change in position of specimens during the study. In our study, while histopathological findings following treatment revealed *H. pylori* positivity in 18 (39.1%) patients, control PCR testing showed the presence of *H. pylori* in 26 (56.5%) patients. Also with DNA sequencing analysis, we found point mutations in *H. pylori* that led to clarithromycin resistance in six of these patients. According to the results of melting curve analysis, two of the four patients who showed resistance to clarithromycin after PCR prior to treatment were found to have *H. pylori* positivity after treatment. This finding was confirmed by histopathology: positive *H. pylori* results were observed from both histopathological evaluation and PCR analysis conducted in all four patients post treatment. After DNA sequencing analysis studies, histopathology results revealed *H. pylori* positivity in 3 of the 9 patients in whom mutant genes were detected before treatment, whereas 4 of the 6 patients who had mutant genes after treatment still showed *H. pylori* positivity.

A close look at the results of existing studies reveals that, irrespective of the method used in determining clarithromycin resistance or sensitivity, in patients who have tested positive for *H. pylori* undergoing first line treatment with clarithromycin based triple therapy, complete eradication can either be achieved in resistant cases or fail in sensitive cases.[25-29] This finding clearly shows that current methods used in determining clarithromycin susceptibility posses existing flaws that need to be addressed.

CONCLUSION

The aim of determining clarithromycin resistance before treatment we were able to show that, results from both the PCR and Melting Curve Analysis method may not be solely true or reliable. From this perspective, we inferred that in determining clarithromycin resistance via molecular methods, instead of using the Melting Curve Analysis method only, combining it with other methods such as DNA sequencing analysis may be useful. In the light of the current study, we are of the view that, further development and improvements in the Melting Curve Analysis Method for determining clarithromycin resistance in microbiology laboratories could be useful, as well as cost and time effective, in clinical practice and as such play a larger role in patient care.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out as thesis study in 1999.

Informed Consent: Due to the nature of the study, informed consent is not required.

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

Relationship between thyroid function tests and bioelectrical impedance measurement parameters according to degree of obesity

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ABSTRACT

Aims: This study aimed to investigate the relationship between thyroid function tests and bioelectrical impedance measurement parameters showing body composition in groups of patients with varying degrees of obesity as determined by body mass index (BMI).

Methods: A total of 120 people between the ages of 18 and 65 years were enrolled in the study, including 20 individuals with stage 1 obesity, 20 with Stage 2 obesity, 20 with Stage 3 obesity, and 40 with normal body weights. In the collection of data, a case report form prepared by the researcher for gathering information about the participants and the results of blood tests and bioelectrical impedance measurements made with a Tanita device were used. Blood samples were taken from the antecubital vein between 09:00 and 10:00 in the morning after at least 8 hours of fasting. HOMA-IR values were calculated by measuring fasting plasma glucose and insulin.

Results: No significant correlation was found between median BMI and TSH, fT3 and fT4 levels in the whole population. While a negative correlation was found between median TSH and BMI in the group with normal body weight (r=-0.430, p=0.006), a positive correlation was found in the Stage 1 obese group (r=0.553, p=0.011). This relationship was not significant in the Stage 2 and morbidly obese groups. There was no significant correlation between BMI and fT4 and fT3 in all groups. A positive correlation was found between fat percentage and TSH (r=0.391, p=0.014) and fT3 (r=0.333, p=0.038) levels in the group with normal body weight, while no correlation was found with T4 levels.

Conclusion: No statistically significant differenceswere found in terms of thyroid functions in different obesity classes as determined by BMI. Elevations of thyroid-stimulating hormone in obese patients are thought to be a result of obesity, not the cause.

Keywords: Obesity, morbid obesity, thyroid, free T3, free T4, thyroid-stimulating hormone

INTRODUCTION

Although the morbidities caused by obesity have been known since 2500 BC, its prevalence hasbeen gradually increasing throughout history.[1] Obesity, a chronic disease, is an epidemic public health problem. Its prevalence is regularly monitored in most countries due to its increasing incidence. Its prevalence in the United States was stated to be between 20.2% and 36.2%.[2] In another study conducted in the United States, it was reported that it had increased from 22.9% to 34.9% between 1988 and 2012.[3] The findings in Turkey are similar, as the prevalence of obesity was found to be approximately 32% in the TURDEP II study, in which 26,499 individuals were evaluated.[4]

Considering that obesity causes many complications such as atherosclerosis, malignancy, cardiovascular diseases, metabolic syndrome, respiratory failure, and diabetes, its impact on public health is significant and it constitutes the basis of serious health expenditures.[5,6]

Various methods are used in the evaluation of obesity. Anthropometric measurements, body mass index (BMI), and body components evaluated by assistive devices are frequently preferred because they are easy and fast to apply and they do not entail radiation. In addition, measurements of body fat or water percentage by computed tomography, magnetic resonance imaging, ordual-energy X-ray absorptiometry (DXA) may also be used.

Thyroid hormones regulate the metabolic processes necessary for normal growth and development.[7] It is known that thyroid hormone levels are closely related to body weight and energy expenditure. Since a hypermetabolic state occurs in hyperthyroidism, defined asexcessive levels of thyroid hormones, resting energy expenditures increase, weight loss is observed, cholesterol levels decrease, and lipolysis and gluconeogenesis increase.[7] On the contrary, in hypothyroidism, which is defined as a decrease in thyroid

hormones, resting energy expenditures decrease, weight gain is observed, cholesterol levels increase, and lipolysis and gluconeogenesis decrease.[10] It has been stated that even slight variations from the reference range in thyroid functions can cause weight gain and the development of localized obesity.[11] Thyroid-stimulating hormone (TSH) levels in obese children, adolescents, and adults have been shown to be at the upper end of the normal range or slightly elevated.[12]

Bioelectrical impedance measurements, which are frequently utilized for both practical and research purposes, can be used to evaluate total body water, total fat percentage, and the difference between them. Body fat percentage is thought to correlate better with obesity-related health risks compared to BMI.[5,6] The present study was undertaken to investigate the relationships between thyroid function tests and bioelectrical impedance measurement parameters showing body composition among patients with varying degrees of obesity as determined by BMI.

METHODS

Ethics

The study was carried out with the permission of Kırıkkale University Faculty of Medicine Clinical Researches Ethics Committee (Date: 29.11.2016, Decision No: 23/04). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Purpose and Type of Research

This study aimed to evaluate the effect of thyroid hormones on the differences in bioelectrical impedance measurement parameters among different obesity groups.

Place and Time of Research

Our research was conducted on patients who applied to the diabetes-obesity outpatient clinic of Kırıkkale University Faculty of Medicine between 29.11.2016 and 30.12.2016.

Population and Sample of the Research

A total of 120 people between the ages of 18 and 65 years were enrolled in the study, including 20 individuals with stage 1 obesity, 20 with stage 2 obesity, 20 with stage 3 obesity, and 40 with normal body weight. Obesity was evaluated with BMI, a common screening tool calculated with the formula of body weight (kg)/height (m^2). BMI values of <18.5 kg/m^2 reflect underweight, 18.5-24.9 kg/m^2 normal weight, 25-29.9 kg/m^2 overweight, 30-34.9 kg/m^2 class 1 obesity, 35-39.9 kg/m^2 class 2 obesity, and ≥40 class 3 or morbid obesity.[13]

Inclusion Criteria for Research

1. Those between the ages of 18-65
2. BMI of ≥25 kg/m^2 (being overweight or obese) for patients and BMI of 18-24.9 kg/m^2 for the control group
3. Not using steroids or hormonal therapy for any reason
4. Not having an eating disorder such as bulimia or anorexia nervosa
5. Volunteer by signing the informed consent form

Exclusion Criteria

1. Those who are not between the ages of 18-65
2. Refusing to participate in the study
3. Having a communication difficulty
4. Presence of Diabetes mellitus
5. Using steroids or hormonal therapy for any reason
6. Presence of chronic liver or kidney disease
7. Use of orlistat or a similar drug that inhibits fat absorption
8. Having thyroid disease and using a thyroid hormone or anti-thyroid agent, or having a history of thyroid hormone or anti-thyroid agent use, or a history of antidepressant or antipsychotic drug use
9. Pregnancy
10. Malignancy
11. Engaging in another study

Data Collection Tools

In the collection of data, a case report form prepared by the researcher for gathering information about the participants and the results of blood tests (TSH, free T3 [fT3], free T4 [fT4], insulin, HOMA-IR, fasting blood glucose [FBG], low-density lipoprotein cholesterol [LDL]) and bioelectrical impedance measurements made with a Tanita device (Tanita BC-420 MA) were used. Blood samples were taken from the antecubital vein between 09:00 and 10:00 in the morning after at least 8 hours of fasting. HOMA-IR values were calculated by measuring fasting plasma glucose and insulin. The formula was as follows: HOMA-IR=fasting plasma glucose (mmol/L) × fasting plasma insulin (mUmL)/22.5.

Case Report Form for Personal and Disease Characteristics

The demographic characteristics (sex and age), laboratory findings (TSH, fT3, fT4, FBG, insulin, HOMA-IR, and LDL) and bioelectrical impedance measurements (height [cm], weight [kg], body mass index [kg/m^2], fat mass [kg], muscle mass [kg], bone mass [kg], fat percentage [%], basal metabolic rate [kcal]) of the participants were recorded in the case report form.

Bioelectrical Impedance Measurements

Bioelectrical impedance analysis was performed with the Tanita-BC 420 MA device. This device has a frequency of 50-60Hz and current of 1.5 A. Its use is based on the difference of the electrical permeability of different tissues. Participants were required to not eat anything for at least 4 hours before the measurementsor drink anything containing caffeine, not enter a sauna or bath or consume alcohol 24 hours before the measurements, and not engage in sports on the day of the measurements. While the measurements were being taken, individuals were asked to stand on the metal surface of the device with bare feet and position their arms parallel to the body. The measurements took approximately 1-2 minutes for each subject and the values of weight, body fat mass, bone mass, fat percentage, and basal metabolic rate determined by the bioelectrical impedance analyzer were output from the device and recorded on the case report forms.

Statistical Analysis

SPSS version 20 package software was used for statistical analysis. Descriptive statistics were presented as numbers, percentages, mean/median and standard deviation. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov, Shapiro-Wilk tests). Numerical variables that did not show normal

distribution were compared using the Kruskal Wallis Test. Correlation between variables was evaluated with Pearson or Spearmen Tests according to normality distribution. Categorical data were compared with the Chi-square test. Confidence interval was set as 95%. P<0.05 was considered statistical significance.

RESULTS

The median age did not differ significantly between the groups (p=0.18). Demographic characteristics are presented in **Table 1**.

Table 1. Demographic characteristics of the obesity groups and the normal weight group

	Group 1 (n=40) (BMI normal)	Group 2 (n=20) (BMI 30-34.9 kg/m²)	Group 3 (n=20) (BMI 35-39.9 kg/m²)	Group 4(n=20) (BMI ≥40 kg/m²)	P value
Gender, n (%)					0.052
Male	13(32.5)	4(20)	1(5)	2(10)	
Female	27(67.5)	16(80)	19(95)	18(90)	
Age, years	38.35±10.4	37.45±11.04	42.60±10.26	46.15±12.23	0.180

The median TSH, median fT3 and median fT4 did not differ significantly between the groups. While the Median insulin level was higher in group 4, the lowest level was found in group 1. The median insulin level did not differ significantly between group 2 and group 3 (**Table 2**, **Figure 1**). The median HOMA-IR, median FBG and median LDL levels differed significantly between the groups (p<0.05) (**Table 2**).

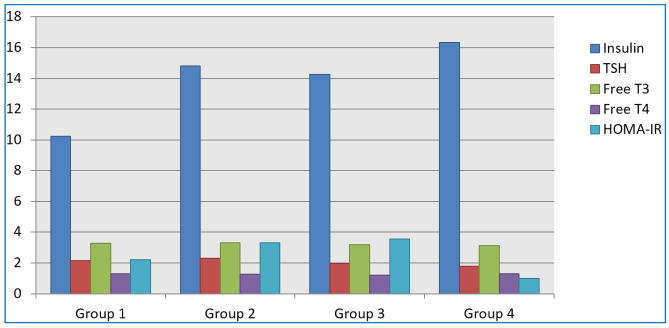

Figure 1. Insulin, HOMA-IR, TSH, free T3 and free T4 values of the groups

The medianfat mass level was significantly different between all groups (p<0.001), and the fat mass linearly increased as increased the degree of obesity. While medianmuscle mass and the median bone mass levels were significantly different in Group 1 and Group 4 compared to other groups, these parameters were higher in group 4 compared to Group 1 (p<0.05). The medianfat percentages was significantly different between all groups (p<0.001), and the fat percentages linearly increased as increased the degree of obesity. The medianbasal metabolic rate was lower in Group 1 compared to Group 2 (p=0.025) and Group 4 (p<0.001), while it was higher in Group 4 compared to Group 3 (p=0.043).

No significant correlation was found between BMI and TSH, fT3 and fT4 levels in the whole population. There was a negative correlation between BMI and TSH in the group with normal body weight (r=-0.430, p=0.006), while no correlation was found between BMI and fT3 (r=0.064, p=0.696) and fT4 (r=0.003, p=0.985). While there was a positive correlation between TSH and BMI in the stage 1 obese group (r=0.553, p=0.011), no significant correlation was found between BMI and T4 (r=-0.193, p=0.415) and T3 (r=0.008, p=0.974). There was no significant correlation between BMI and TSH (r=0.147, p=0.537), T4 (r=-0.346, p=0.136) and T3 (r=-0.267, p=0.256) in the stage 2 obese group. There was no significant correlation between BMI and TSH (r=-0.267, p=0.256), T4 (r=-0.267, p=0.256) and T3 (r=0.060, p=0.801) levels in the morbidly obese group.

While there was a positive correlation between fat percentage and TSH (r=0.391, p=0.014) and T3 (r=0.333, p=0.038) levels in the group with normal body weight, no significant correlation was found with T4 (r=0.037, p=0.821). In the stage 1 obese group, there was a positive correlation between fat percentage and T3 (r=0.521, p=0.018) levels, but no significant correlation was found between fat percentage and TSH (r=0.129, p=0.589) and T4 (r=-0.345, p=0.136) levels. There was no significant correlation between fat percentage and TSH (r=0.326, p=0.161), T4 (r=0.059, p=0.806) and T3 (r=-0.336, p=0.113) levels in the stage 2 obese group. There was no significant correlation between fat percentage and TSH (r=-0.117, p=0.456), T4 (r=0.272, p=0.246) and T3 (r=0.242, p=0.304) levels in the morbid obese group.

There was no significant correlation between HOMA-IR and TSH (r=-0.094, p=0.563), T4 (r=0.189, p=0.242) and T3 (r=0.141, p=0.386) levels in the group with normal body weight. In the stage 1 obese group, there was a positive correlation between HOMA-IR and T3 (r=0.512, p=0.021) levels, but no significant correlation was found between HOMA-IR and TSH (r=0.303, p=0.194) and T4 (r=0.043, p=0.857) levels. There was no significant correlation between HOMA-IR and TSH (r=0.123, p=0.607), T4 (r=-0.114, p=0.631) and T3 (r=0.115, p=0.630) levels in the stage 2 obese group. There was no significant correlation between HOMA-IR and (r=-0.428, p=0.060), T4 (r=0.073, p=0.761) and T3 (r=0.182, p=0.442) levels in the morbid obese group.

There was no significant correlation between LDL and TSH (r=-0.206, p=0.202), T4 (r=0.069 p=0.674) and T3 (r=-0.124, p=0.445) levels in the group with normal body weight. In the stage 1 obese group, there was a positive correlation between LDL and TSH (r=0.469, p=0.037) levels, but no significant correlation was found between LDL and T4 (r=0.005 p=0.983) and T3 (r=0.153, p=0.519) levels. In the stage 2 obese group, there was a positive correlation between

Table 2. TSH, fT3 and fT4, insulin, HOMA-IR, fasting blood glucose and LDL results of the groups

	Group 1 (n=40) (BMI normal)	Group 2 (n=20) (BMI 30-34.9 kg/m²)	Group 3 (n=20) (BMI 35-39.9 kg/m²)	Group 4 (n=20) (BMI ≥40 kg/m²)	P value
TSH, µU/mL	2.14±1.26	2.31±1.08	1.97±1.18	1.79±0.97	0.585
fT3, pg/mL	3.27±0.49	3.32±0.38	3.19±0.46	3.12±0.43	0.274
fT4, ng/dL	1.31±0.15	1.27±0.18	1.22±0.17	1.29±0.20	0.222
Insulin, µU/mL	10.23±4.10	14.80±7.87	14.25±8.20	16.33±6.32	0.002
HOMA-IR	2.22±0.90	3.31±1.64	3.56±2.13	4.06±1.85	<0.001
FBG, mg/dL	88.02±7.78	92.37±11.47	97.55±12.93	100.05±10.64	<0.001
LDL, mg/dL	87.53±29.10	104.90±27.69	107.15±25.67	124±71.57	0.013

LDL and TSH (r=0.621, p=0.003) levels, but no significant correlation was found between LDL and T4 (r=0.113 p=0.634) and T3 (r=0.271, p=0.248) levels. In the morbid obese group, there was a negative correlation between LDL and T4 (r=-0.485, p=0.030) levels, but no significant correlation was found between LDL and TSH (r=-0.047 p=0.845) and T3 (r=-0.167, p=0.480) levels.

In the group with normal body weight, there was a positive correlation between basal metabolic rate and T3 (r=0.414, p=0.009) levels, but no significant correlation was found between basal metabolic rate and TSH (r=-0.050, p=0.764) and T4 (r=0.143, p=0.384) levels. In the stage 1 obese group, there was no significant correlation between basal metabolic rate and TSH (r=0.176, p=0.458), T4 (r=0.173, p=0.466) and T3 (r=0.315, p=0.176) levels. In the stage 2 obese group, there was no significant correlation between basal metabolic rate and TSH (r=0.078, p=0.743), T4 (r=0.111 p=0.643) and T3 (r=-0.032, p=0.895) levels. In the morbid obese group, there was no significant correlation between basal metabolic rate and TSH (r=0.218, p=0.356), T4 (r=-0.201, p=0.396) and T3 (r=-0.032, p=0.895) levels.

In the group with normal body weight, there was a positive correlation between fat mass and TSH (r=0.447, p=0.004) levels, but no significant correlation was found between basal metabolic rate and T4 (r=0.125 p=0.448) and T3 (r=-0.251, p=0.124) levels. In the stage 1 obese group, there was a positive correlation between fat mass and T3 (r=0.543, p=0.013) levels, but no significant correlation was found between basal metabolic rate and TSH (r=0.133, p=0.577) and T4 (r=0.358, p=0.121) levels. In the stage 2 obese group, there was no significant correlation between fat mass and TSH (r=0.323, p=0.165), T4 (r=0.151 p=0.525) and T3 (r=-0.417, p=0.068) levels. In the morbid obese group, there was no significant correlation between fat mass and TSH (r=0.089, p=0.708), T4 (r=0.009, p=0.971) and T3 (r=0.013, p=0.957) levels.

DISCUSSION

When the relationships between thyroid functions and body compositions were evaluated, a positive correlation was found between fT3 and fat percentage among participants with stage 1 obesity(r=0.521, p=0.018), and a positive correlation was also found between fat mass and fT3 (r=0.543, p=0.013). However, this relationship could not be shown in other BMI groups. To our knowledge, there are limited studies evaluating the relationships between thyroid hormones and body compositions in obese patients. In a study conducted with euthyroid men, including obese patients, 1001 individuals were evaluated and a positive correlation was shown between fT3 and fat mass,[14] consistent with our findings. In another study conducted in 2014, it was reported that there was a positive correlation between fT3 and body fat mass in euthyroid overweight and obese participants, regardless of age and gender, but no significant correlation was found for fT4.[15] Two mechanisms are generally held responsible for the relationship between fT3 and fat mass. First, in obese individuals, circulating leptin levelsare increased and peripheral adipocyte amountsare proportionally related to leptin levels.[16] At the same time, leptin accelerates the conversion of T4 to T3. Second, insulin levels are also higher in obese individuals and insulin resistance is higher compared to those with normal BMI. In an animal study, it was reported that deiodinase activity in adipocyte tissues increased with increased insulin.[17] These factors explain the relationship between fT3 and fat mass. As expected, in our study, it was observed that the percentages of fat and fat mass increased as the degree of obesity increased (p<0.001).

In our study, no significant relationship was found between the participants in different obesity classes as evaluated by BMI in terms of thyroid functions (TSH, fT3 and fT4). Similarly, when the obese groups and the control group were compared, no significant differenceswere found between groups in terms of TSH, fT3,or fT4 levels.

Among the BMI groups, there was an inverse relationship between BMI and TSH only in the control group, while a positive correlation was found in patients with stage 1 obesity. No correlation was found between BMI and TSH or T3 in the other body weight groups. The finding of no relationship between BMI and fT4 in our study is confirmed by most other studies in the literature, but contrary to our findings, it has been reported in many studies that BMI and TSH or fT3 levels in obese individuals vary compared to healthy controls.In the study by Knudsen et al.,[11] it was reported that there was no relationship between BMI and fT3, consistent with our study. A study by Manji et al.[18] conducted with 401 euthyroid patients reported that TSH and fT4 levels did not differ between obese and healthy controls, similar to our study. A study by Chomardet al.[19] reported that fT4 levels did not differ between obese and healthy controls. Previous studies by Gusekko et al.[20] and Hak et al.[21] reported that obesity did not affect fT4 values.Another study from 2014 reported similar thyroid hormone levels in overweight and obese participants.[15]

There are also many studies with results opposite to our finding that fT3 levels do not change in obese patients. In a study conducted by Reinehr et al.[22] in 2006, it was reported that TSH and fT3 concentrations increased in obese patients while fT4 levels did not change.In another study in which 6164 participants were evaluated, it was shown that serum TSH levels and BMI were positively correlated.[23] Parallel to these findings, Knudsen et al.[11] evaluated 4649 participants in a cross-sectional study and showed a positive correlation between BMI and serum TSH and a negative correlation between BMI and fT4. There are many studies showing a positive relationship between BMI and TSH.[24-27] The reasons forthis relationship are not fully known; however, some theories have been suggested. Among them, the leading mechanism is proposed to be the increase in deiodinase activity in obese individuals. It has been suggested that the conversion of T4 to T3 in obese individuals createsa defense mechanism against increasing energy needs.[28,29] Another theory is that leptin produced from adipocytes accelerates T3 conversion by increasing deiodinase activity.[30] Finally, it has been suggested that inflammatory cytokines increase in obesity and that increased cytokines inhibit sodium or iodine transporters, resulting in a secondary TSH increase.[31] The small number of participants in our study may have masked the relationship between obesity and fT3.

TSH elevations in obese patients are thought to be a result of obesity, not the cause. In a study conducted with adolescents in which patients were followed for 1 year, it was shown that TSH and fT3 levels decreased to normal ranges in those who reached the target of significant weight loss, but they did not change in those who did not achieve significant

weight loss.[22] Similarly, in the study conducted by Sarı et al.[32] a decrease in TSH values was reported with more than 10% weight loss. Leptin levels correlate directly with the amount of adipose tissue, and leptin has been reported to stimulate TSH biosynthesis in vitro.[33] In addition, synchronization between leptin and TSH secretion has been reported in both adults[34] and children.[35] However, there are also studies showing no relationship between leptin and TSH.[36] On the other hand, although TSH levels are high in obese individuals, TSH receptors are less expressed in adipocytes. Therefore, peripheral thyroid hormone resistance develops and TSH and fT3 levels increase more. This relationship is reversed as adipocytes return to their normal state with weight loss. In our study, leptin levels could not be evaluated due to technical limitations.

As expected in our study, insulin, HOMA-IR as an indicator of insulin resistance, fasting plasma glucose, and LDL levels increased as BMI increased. When the relationships between thyroid functions and LDL concentrations were evaluated, a positive relationship was found between TSH and LDL in the group with stage 1 obesity, and a negative relationship was found between fT4 and LDL in the morbidly obese group. In hypothyroidism, hypercholesterolemia and increased LDL levels are observed due to the decrease in LDL catabolism. In a study conducted with euthyroid patients, it was reported that fT4 levels and LDL levels were negatively correlated, supporting our findings.[37] This relationship was maintained even when adjusted for age and gender. In light of these findings, it can be said that the relationship between thyroid functions and lipid metabolism extends into the euthyroid range. Therefore, low fT4 levels in euthyroid individuals may be associated with cardiovascular risk.

In our study, it was observed that increases in BMI and increases in the basal metabolic rate occurred in parallel. However, when the relationships between thyroid functions and basal metabolic rate were evaluated, no significant relationship was found between basal metabolic rate and TSH, fT4, or fT3 in any of the patient groups. It is known that resting energy expendituresare sensitive to small changes in thyroid functions in patients receiving levothyroxine therapy, and resting energy expenditures are increased in cases of hyperthyroidism and decreased in hypothyroidism. However, this relationship could not be demonstrated in studies conducted with euthyroid individuals. In a study by Tagliaferri et al.[38] similar to our study, it was confirmed that there was no relationship between TSH and resting energy expenditures in obese patients. Resting energy expenditureswere measured by the indirect calorimetric method in these studies. In our study, data were obtained with a formula using lean body mass and age withthe bioelectrical impedance method.

Hypothyroidism and hyperthyroidism are conditions associated with glucose metabolism. It has been reported that insulin resistance is also encountered after T3 administration to healthy volunteers. In a study conducted with euthyroid patients, a negative relationship was shown between HOMA-IR and fT4 while a positive relationship was shown with TSH, and it was also stated that fasting blood glucose and insulin levels were associated with fT4. However, that study did not include obese individuals. In our study, no relationship could be demonstrated between HOMA-IR, insulin,or fasting blood glucose and thyroid functions. This is likely because obesity itself affects glucose metabolism parameters.[39]

Limitations of the study: To our knowledge, the studies conducted to date to evaluate the relationships between thyroid hormones and body compositions in obese patients are very limited. Thyroid functions are affected by factors such as temperature, nutrition, fasting time, and smoking. Although attention was paid to parameters such as hunger and temperature in our study, other possibly related factors were not evaluated. In our study, which was conducted with a total of 120 participants, relationships between obesity and fT3 and TSH levels, frequently shown in the literature, could not be demonstrated. One of the possible reasons for this was the small number of participants. Although the basal metabolic rate is an indirect indicator of resting energy expenditures, considering that calorimetric measurements, which require strict patient preparation, are the gold standard, it may be assumed that evaluations of basal metabolic rate calculations by the bioelectrical impedance method do not fully reflect reality. In calculations of body compositions, methods such as DXA have been used more frequently in the literature and have provided more accurate results. However, it has been reported that bioelectrical impedance results show good correlations with DXA results.[40]

CONCLUSION

In our study, no statistically significant difference was found in terms of thyroid functions (TSH, fT3, and fT4) among participants in different classes of obesity as evaluated by BMI. The small number of participants in our study may have masked the relationship between obesity and fT3. TSH elevations in obese patients are thought to be a result of obesity, not the cause. More extensive studies on this issue are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Faculty of Medicine Clinical Researches Ethics Committee (Date: 29.11.2016, Decision No: 23/04).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

The effect of anthropometric and metabolic parameters on the development of erosive reflux disease in patients with gastroesophageal reflux disease

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ABSTRACT

Aims: Gastroesophageal reflux disease (GERD) is a common health problem worldwide. Previous studies have reported that central obesity associated with visceral steatosis is an important problem in digestive system diseases, especially reflux-related diseases. This study aimed to examine the effect of body fat distribution on the development of erosive esophagitis.

Methods: A total of 131 individuals, 105 patients and 26 healthy volunteers, were included in this study. The FSSG questionnaire was applied to all individuals. Patients with an FSSG questionnaire score of 10 or more underwent upper gastrointestinal tract endoscopy. Patients with esophagitis on endoscopy were included in the erosive esophagitis group, whereas patients without esophagitis were included in the non-erosive group. Serum biochemistry (fasting glucose, insulin, lipid panel, uric acid, TSH, AST, ALT) analyzes were performed. Waist circumference was measured. Body compositions were evaluated using the bioelectrical impedance method (Tanita).

Results: Erosive esophagitis was found in 68 of 105 patients enrolled in the study, and non-erosive esophagitis in 37. There was no statistically significant difference in age, BMI, and waist circumference between the erosive, non-erosive and control groups. The visceral fat percentage was higher in the erosive esophagitis group than the other groups ($p < 0.001$). At the end of the pairwise comparison of the groups, it was found that visceral fat value was higher in the erosive group than the non-erosive and control groups, while the visceral fat value was similar in the control and non-erosive groups. Except for the control group, when comparing the erosive and non-erosive groups, it was found that most of the patients in the erosive group were male, their FFM values and muscle mass were relatively high, and visceral fat values were significantly higher.

Conclusion: An increase in visceral fat is a more important risk factor for the development of erosive esophagitis than obesity, waist circumference and increased BMI.

Keywords: GERD, Erosive esophagitis, FSSG, bioelectrical impedance, visceral fatigue

INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined by the American College of Gastroenterology (ACG) as a group of symptoms or complications that result from the backflow of stomach contents into the oesophagus, mouth, or lungs. GERD has become an increasingly common health problem worldwide, especially in developed countries.[1,2]

Symptoms associated with GERD negatively affect patients' quality of life, performance, and productivity, and result in various losses in the workforce. Because the disease requires long-term treatment, it also imposes a significant economic burden.[3]

GERD is classified based on the appearance of the oesophageal mucosa during upper endoscopy. Erosive esophagitis (ERD) is characterized by the presence of erosions observed endoscopically in the distal oesophageal mucosa. It may be symptomatic or asymptomatic. Non-erosive reflux disease (NERD) is characterized by the presence of GERD symptoms without erosions in the oesophageal mucosa.1 Endoscopic esophagitis is observed in less than 50% of patients with GERD symptoms. Reflux esophagitis is the most common symptom of oesophageal damage.[4]

The aetiology of GERD is multifactorial, but environmental factors are known to play an important role. Obesity, smoking, and certain foods are among the risk factors.[5] Obesity and weight gain are more prominent in patients with ERD than in those with NERD.[6] Abdominal obesity has been identified as an independent risk factor, especially for ERD. Abdominal obesity is also known to increase the symptoms of GERD.[7]

Previous studies have reported that waist circumference is the best indicator of visceral fat tissue among anthropometric measurements and that visceral fat tissue has a greater impact on insulin resistance than subcutaneous fat tissue.[8] Insulin resistance is thought to play an important role in the pathogenesis of ERD. Visceral adipose tissue is biologically active and can secrete pro-inflammatory cytokines, particularly interleukin-6, and tumor necrosis factor-alpha, which can lead to insulin resistance. Furthermore, these cytokines may be associated with chronic inflammatory statesin obesity, increasing the risk of ERD.[9,10]

Epidemiologic studies have indicated that obesity is an important risk factor for the development of GERD and is associated with oesophageal complications such as ERD, Barrett's oesophagus, and oesophageal adenocarcinoma. The fact that obesity rates have almost tripled worldwide since 1975 and the epidemic rate has become a global health problem is a very important problem in terms of GERD. Risk factors associated with ERD are male gender, obesity, especially abdominal visceral obesity, presence of GERD symptoms for more than one year, alcohol consumption, smoking, and presence of hiatal hernia.[11]

We hypothesized that an increase in visceral fat compared to total body fat in patients with gastroesophageal reflux might increase the risk of developing erosive reflux. This study aimed to evaluate the effects of body fat distribution on the development of ERD using a Tanita quantitative method by evaluating metabolic and anthropometric parameters that may affect the development of ERD.

METHODS

Ethical approval was obtained from the Kırıkkale University Clinical Researches Ethics Committee (Date: 26.02.2019, Decision No: 03/04). All procedures were performed in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Selection of Study Population and Data Collection

In this descriptive cross-sectional study, 105 patients who presented with dyspeptic complaints to the Gastroenterology Clinic of Kırıkkale University Faculty of Medicine and 26 healthy volunteers who agreed to participate in the study were included. The Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (FSSG) questionnaire was administered to the patient and the control groups. Patients with an FSSG score of 10 or more underwent upper gastrointestinal system endoscopy.

Inclusion criteria for the study:

1. Consent to participate in the study,
2. Age between 18 and 65 years,
3. Patients with FSSG scores of 10 and above and healthy volunteers with FSSG scores below 8.

Exclusion criteria for the study:

1. Individuals who have a history of using medications that can cause ERD (such as tetracycline)
2. Diabetes mellitus
3. Thyroid dysfunction
4. Chronic obstructive pulmonary disease
5. Chronic kidney disease
6. Patients diagnosed with liver cirrhosis
7. Individuals who have used any herbal products
8. History of abdominal surgery (e.g., cholecystectomy, gastric surgery, colon surgery, reflux surgery, hiatal hernia surgery)
9. Patients with coronary artery disease
10. Patients who have used PPİ or H2 receptor blockers in the last 4 weeks
11. Pregnant patients
12. Patients with hiatal hernia, gastric ulcer, duodenal ulcer, or malignancy detected during endoscopy.

Method and Interpretation of the FSSG Questionnaire

We administered the FSSG questionnaire to 642 patients aged between 18 to 65 years who presented to the gastroenterology clinic with reflux and dyspeptic symptoms and were diagnosed with GERD (**Table 1**). Each question was scored on a scale of 1 to 4 as never (0), rarely (1), sometimes (2), often (3), always (4). Questions related to dyspeptic symptoms were excluded (5 questions), whereas 7 questions related to reflux symptoms were included. A score of ≥10 based on the 7 reflux-related questions was considered as a diagnosis of GERD. Reflux-related symptoms were scored up to 28 points (maximum=7×4), whereas dyspeptic symptoms were scored up to points(maximum=5×5). The total score was calculated as the sum of the reflux-related and dyspeptic

Table 1. F-scale frequency scale for the symptoms of gastroesophageal reflux disease (FSGG)

Do you have any of the following symptoms?					
Name-Surname: Age: Gender: Date:					
Questions	**Mark this section**				
	Never	**Occasionally**	**Sometimes**	**Often**	**Always**
1-Do you get heartburn?					
2-Does your stomach get bloated?					
3-Does your stomach ever feel heavy after meals?					
4-Do you sometimes subconsciously rub your chest with your hand?					
5-Do you ever feel sick after meals?					
6-Do you get heartburn after meals?					
7- Do you have an unusual (e.g. burning) sensation in your throat?					
8-Do you feel full while eating meals?					
9-Do you things get stuck when your swallow?					
10-Do you get bitter liquid (acid) coming up into your throat?					
11-Do you burp a lot?					
12-Do you get heartburn if you bend over?					

symptom scores. Extra-oesophageal symptoms (chronic cough, chest pain, hoarseness, sore throat, apnea, choking sensation, teeth grinding) were assessed by questionnaire form. An FSSG score of 10 or more was found in 105 of 642 patients. , Descriptive information such as age, gender, employment status, smoking and alcohol consumption, and the presence of hypertension, about these patients was collected by questionnaire.

Endoscopic Evaluation and Classification of Esophagitis

Upper gastrointestinal endoscopy was performed in patients an FSSG score of 10 and above, which is an indication for endoscopy. The severity of ERD was graded A to D according to the Los Angeles esophagitis classification (Table 2).

Table 2. Los Angeles classification

Grade A	≤5 mm mucosal damage in mucosal folds
Grade B	Damage >5 mm in mucosal folds but no continuity between folds
Grade C	Mucosal damage between 2 or more mucosal folds continuous, but not all around
Grade D	All-round mucosal damage (in the oesophageal lumen) more than 75%)

Grade A reflux esophagitis was found in 68 patients. A total of 37 patients without esophagitis were considered as NERDpatients. Among the 146 patients with an FSSG score of 10 or more were excluded from the study because of pangastritis, duodenal ulcer, gastric ulcer, or hiatal hernia on upper gastrointestinal system endoscopy.

Anthropometric Measurements and Tanita

Anthropometric assessment of all participants was performed using the Tanita method (Bioelectrical Impedance) in a standing upright, looking straight ahead with eyes, wearing light clothing, barefoot, and removing all metallic accessories.All participants were instructed to notconsume any food or drink for at least 4-5 hours prior to the test, to avoid exercisein 12 hours before the test, and not consume any food or drink containing alcohol or caffeine in the 24 hours prior to the test. Measurements of height, weight, (BMI), percentage of body fat, fat mass (kg), Fat-Free Mass(FFM), muscle mass (kg), Total Body Water(TBW), percentage of TBW, bone mass (bone mineral weight), Basal Metabolic Rate(BMR), metabolic age, visceral fat rating, and degree of obesity were obtained using the Tanita method. The waist circumference of all participants were measured in the standing position with an inelastic tape measure by assessing the Costas and the longest horizontal diameter passing through both iliac crests.

Laboratory Analysis Methods

Laboratory tests such as fasting glucose, insulin, TSH, AST, ALT, HDL, LDL, triglycerides, and total cholesterol were performed in patients after at least 10 hours of fasting. The HOMA-IR index were calculated as: HOMA-IR=fasting glucose × fasting insulin/405.

Statistical Analysis

Statistical analyses of collected data were conducted using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Determination of the normally distributed data was conducted using the Kolmogorov-Smirnov test. Numerical variables that had normal distribution were expressed as the mean ± standard deviation, while those with non-normal distribution were expressed as the median (min-max). For comparisons between groups, Student's T test and ANOVA test (post-hoc test: Bonferroni test) were used for parametric data, whereas Mann-Whitney U test and Kruskall-Wallis test (post-hoc test: Dunn's test) were used for non-parametric data. Correlation analysis was performed using the Spearman's correlation test. Multivariable logistic analyses were conducted to establish any possible independent predictors of erosive reflux. Diagnostic performance analysis was performed with ROC Curve analysis. $P < 0.05$ was taken as statistical significance.

RESULTS

The mean age of the control group was 44.11±8.49 years, with a gender distribution of 9 females (6.9%) and 17 males (13%). The mean age of the ERD group was 45.34±10.29 years, with a gender distribution of 20 females (15.3%) and 48 males (36.6%). The mean age of the NERD group was 43.92±13.89 years, with a gender distribution of 13 females (9.9%) and 24 males (18.3%). There was no significant difference in age between the groups (p>0.05).The rate of patients working in any occupation was higher in the ERD group compared to the other groups (ERD group=35.9% vs. NERD group=10.7% vs. Control group= 5.3%, p<0.001). The rate of smokers was higher in the ERD group compared to the other groups (ERD group=15.3% vs. NERD group=1.5% vs. Control group= 7.6%, p=0.004). The rate of hypertensive patients was higher in the ERD group compared to the other groups (ERD group=8.4% vs. NERD group=0% vs. Control group= 0%, p=0.004) (Table 3).

Table 3. Comparison of sociodemographic data of the erosive and non-erosive group

Variable	Control	Erosive	Nonerosive	t/Z/x²	p
Age (year) mean±SD	44.11±8.49	45.34±10.29	43.92±13.89	0.239[a]	0.788
Gender n (%)				0.458[‡]	0.796
Female	9 (6.9%)	20 (15.3%)	13 (9.9%)		
Male	17 (13%)	48 (36.6%)	24 (18.3%)		
Profession				17.503[‡]	<0.001
Not working	19 (14.5%)	21 (16.0%)	23 (17.6%)		
Working	7 (5.3%)	47 (35.9%)	14 (10.7%)		
Smoking n (%)				10.941[‡]	0.004
No	16 (12.2%)	48 (36.6%)	35 (26.7%)		
Yes	10 (7.6%)	20 (15.3%)	2 (1.5%)		
Alcohol n (%)				4.462[‡]	0.107
No	24 (18.3%)	67 (51.1%)	37 (28.2%)		
Yes	2 (1.5%)	1 (0.8%)	0 (0.0%)		
Hypertension n (%)				11.125[‡]	0.004
No	26 (19.8%)	57 (43.5%)	37 (28.2%)		
Yes	0 (0.0%)	11 (8.4%)	0 (0.0%)		

(*) Independent Samples t test. (†) Mann Whitney U test. (‡) Pearson Chi-Square test

Mean BMI level did not differ significantly between the groups (ERD group=28.16±3.73 vs. NERD group=27.62±5.76 vs. Control group=27.95±1.62 kg/m2, p=0.819). Mean waist circumference level did not differ significantly between the groups (ERD group=97.57±11.70 vs. NERD group= 97.62±5.76 vs. Control group=96.19±14.13 cm, p=0.876).

Median FFM value was higher in the ERD group compared to the other groups (ERD group=56.75 [range: 32.70-79.0] vs. NERD group=47.10 [range: 35-81] vs. Control

group=47.80 [range: 35-78.70], p=0.036). Median muscular mass value was higher in the ERD group compared to the other groups (ERD group=53.85 [range: 31-75.10] vs. NERD group=47.70 [range: 33.30-77.40] vs. Control group= 47.55 [range: 36.60-74.80], p=0.047). Median visceral fat value was higher in the ERD group compared to the other groups (ERD group=11.5 [range: 6-27] vs. NERD group=9 [range: 1-21] vs. Control group= 8 [range: 3-18], p=0.001). These findings were similar in the NERD and control groups (Table 4).

Table 4. Comparison analysis of Tanita values between groups

Variables	Group(I/J)	Z	p
FFM			
	Control/NERD	-0.216	0.829
	Control /ERD	-2.211	0.027
	NERD / ERD	-1.979	0.048
Muscular mass			
	Control / NERD	-0.265	0.791
	Control / ERD	-2.025	0.043
	NERD / ERD	-1.989	0.047
Visceral fat			
	Control / NERD	-0.161	0.872
	Control / ERD	-3.517	<0.001
	NERD / ERD	-3.434	0.001

Excluding the control group, the rate of males (X2=15.035, p<0.001), the ratio of working in a business sector (X2=9.630, p=0.002), the rate of smoking (X2=8.338, p=0.004), and the rate of hypertension (X2 =6.686, p=0.010) was higher in the ERD group than the NERD group. Excluding the control group, the rate of males in the ERD group (X2=15.035, p<0.001), the rate of those working in a business sector (X2=9.630, p=0.002), the rate of smoking (X2=8.338, p=0.004), and the rate of hypertension (X2=6.686, p=0.010) was higher than the NERD group. In this patient group, FFM values (Z=-1.979, p=0.048) and muscle mass (Z=-1.989, p=0.047) were found to be relatively high, while visceral fat values were found to be significantly higher (Z=-4.309, p<0.001).

As a result of the correlation analysis, visceral fat value and age (r=0.376, p<0.001), gender (r=0.407, p<0.001), glucose level (r=0.294, p=0.002), triglyceride level (r=0.266, p). =0.006), body weight (r=0.498, p<0.001), BMI value (r=0.449, p<0.001), waist circumference measurement value (r=0.451, p<0.001), fat mass value (r=0.368, p<0.001), FFM value (r=0.313, p=0.001), muscle mass value (r=0.312, p=0.001), TBV value (r=0.352, p<0.001), bone mass value (r=0.291, p=0.003), BMR value (r=0.329, p=0.001), metabolic age (r=0.471, p<0.001) and obesity degree (r=0.446, p<0.001) were found to be positively correlated. In addition, body weight and gender (r=0.428, p<0.001), glucose level (r=0.260, p=0.007), insulin level (r=0.235, p=0.016), triglyceride level (r=0.285, p=0.003), ALT level (r=0.200, p=0.041), height (r=0.454, p<0.001), BMI value (r=0.690, p<0.001), waist circumference measurement value (r=0.693, p<0.001), fat mass value (r=0.520, p<0.001), FFM value (r=0.718, p<0.001), muscle mass value (r=0.718, p<0.001), TBV value (r=0.736, p<0.001), positive between bone mass value (r=0.713, p<0.001), BMR value (r=0.760, p<0.001), metabolic age (r=0.416, p<0.001), obesity grade (r=0.686, p<0.001) were found to be positively correlated.

Diagnostic performance of the variables in diagnosing ERD was examined with the ROC-Curve test. According to this; male gender 69% specificity and 70% sensitivity (area=0.697, p=0.001), smoking 30% sensitivity and 94% specificity (area=0.380, p=0.030), 63% sensitivity and 62% for body weight >75 kg specificity (area=0.629, p=0.030), 56% specificity and 57% sensitivity for glucose level >91.50 mg/dL (area=0.625, p=0.034), 65% sensitivity and 54% specificity for FFM value >52.1% (area) =0.617, p=0.048), 58% sensitivity and 62% specificity for muscle mass value >51.75 (area=0.618, p=0.047) and 88% sensitivity and 51% specificity for visceral fat value >8.5 (area=0.629, p =0.030) were found to exhibit diagnostic performance (Table 5).

Table 5. Comparison of biochemical data of erosive-nonerosive groups

Variable			t/ Z/ x^2	p
Glucose median (min-max)/	92.50 (67-199)	89 (60-122)	-2.118†	0.086
Triglyceride median (min-max)/	113.50 (43-463)	99.80 (43-341)	-1.224†	0.221
Total cholesterol mean±SD/	193.87±43.07	194.19±35.13	-0.039*	0.969
HDL mean±SS/	51.24±13.87	53.82±13.26	-0.925*	0.357
LDL mean±SS/	113.31±38.33	118.46±28.46	-0.716*	0.475
TSH median (min-max)/	1.55 (0.01-6.30)	1.80 (0.40-4.10)	-1.470†	0.142
ALT median (min-max)/	19 (8-58)	16 (6-84)	-1.958†	0.050
AST median (min-max)/	17.50 (10-50)	16 (8-34)	-1.363†	0.173
IInsulin median (min-max)/	8.15 (1.30-115)	8 (1-38)	-1.016†	0.310
BMI mean±SD/	28.38±3.68	27.86±5.28	0.587*	0.559
BMR median (min-max)/	6964.50 (4540-10046)	6100 (4556-10075)	-1.855†	0.064
Weist circumference mean±SD/	97.53±11.70	97.62±12.47	-0.038*	0.970
Metabolic age mean±SD/	51.51±15.92	45.95±19.01	1.598*	0.113
TBW percent mean±SD/	50.17±5.79	49.78±8.77	0.274*	0.785
FFM median (min-max)/	56.75 (32.70-79)	47.10 (35-81)	-1.979†	0.048
Fat percent median (min-max)/	27.75 (12.30-54.70)	30.80 (3-45.50)	-0.295†	0.768
Fatmass mean±SD/	23.03±8.26	22.73±10.32	0.162*	0.871
Musclemasss median (min-max)/	53.85 (31-75.10)	44.70 (33.30-77.40)	-1.989†	0.047
Bonemass median (min-max)/	2.85 (1.70-3.90)	2.40 (1.80-4.94)	-1.591†	0.112
Visceral fat median (min-max)/	11.50 (6-27)	8.00 (1-18)	-4.309†	<0.001
Obesity grade mean±SD/	29.16±16.82	27.04±24.10	0.528*	0.598
HOMA-IR median (min-max)/	1.95 (0.26-8.57)	1.68 (0.18-7.04)	-1.311†	0.190

HDL; High density lipoprotein, LDL; Low density lipoprotein, TSH: Thyroid stimulant hormone, ALT; Alanin aminotranspherase, AST; Aspartate aminotranspherase, BMI: Body mass index, BMR: Basal metabolic rate, TBW: Total body water, FFM: Fat-free mass, HOMA-IR: Homeostasis model assessment-insulin resistance

Multivariate logistic regression analysis showed that gender (B= -1.438, Wald=9.223, p=0.002), smoking (B=-1.672, Wald=4.275, p=0.039), body weight (B=-0.061, Wald=6.235, showed that visceral fat value (B=-0.365, Wald=17.811, p<0.001) and degree of obesity (B=0.033, Wald=4.814, p=0.028) were independent predictors of increasing risk of ERD (**Tablo 6**).

Table 6. Logistic regretion analysis

Değişken	B	Wald	p
Cinsiyet (Step 6)	-1.438	9.223	0.002
Sigara kullanımı (Step 6)	1.672	4.275	0.039
Kilo (Step 3)	-0.061	6.235	0.013
Viseral yağ (Step 6)	-0.365	17.811	<0.001
Obezite derecesi (Step 6)	0.033	4.814	0.028

DISCUSSION

Gastroesophageal reflux disease and its complications including ERD, Barrett's oesophagus, and oesophageal adenocarcinoma are increasing worldwide.[12,13] Obesity plays an important role in the development of GERD by impairing the function of the lower oesophageal sphincter, increasing stomachacid and intra-abdominal pressure.[14] Recent studies have shown that transient lower oesophageal sphincter relaxations (TLESRs) is the most important factor in the pathophysiology of GERD. TLESR is the most common reflux mechanism in patients with normal sphincter pressure. It occurs independently of swallowing, is not association with oesophageal peristalsis, lasts longer (>10 seconds) than LES relaxation associated with swallowing, and is associated with inhibition of the crural diaphragm.[15]

In a systematic meta-analysis including 12 population-based studies, 8 studies from Asian countries, 2 from Europe, and 1 from the United States, evaluating the data of 67056 patients between 1997 and 2011, reflux esophagitis was found to occur less frequentlyin femalethan in male. Male gender was identified as an independent risk factor for ERD.[16] In a study conducted by Nam et al.[17] the effects of dietary factors on erosive and non-erosive reflux in 11690 people in Korea in 2017, and it was reported that erosive reflux was more common in male, while non-erosive reflux was more common in female. In a study by Nurleili et al.[18] male formed the majority in the group with ERD, while female formed the majority in the group with NERD. They explained this by the fact that female are more aware of the symptoms compared to male.[18] In the experimental study conducted by Masaka et al.[19] The effects of gender on the risk of developing ERD in and the controlling effect of oestrogen on oesophageal mucosal damage were investigated. It has been reported that oestrogen has an anti-inflammatory effect that can modulate the immune system, such as cell activation and proliferation, cytokine production, and wound healing. This has been suggested as the reason for the lower incidence of erosive esophagitis in female than male. In the present study, which is consistent with the literature,the majority of patientsthe ERD are male, and the majority of the NERD group are female.A study by Chung et al.[20] reported that smoking, alcohol consumption, and metabolic syndrome were associated with an increased risk of reflux esophagitis. In a study of 9840 asymptomatic Japanese male patients conducted by Gunji et al.[21] ERD was found in 1831 patients, and factors such as alcohol, smoking, metabolic changes and hiatal hernia were shown to increase the risk of ERD. Consistent with the literature, we found that smoking increased the risk of ERD, but we found no association with alcohol consumption. This could be due to the small number of patients who consume alcohol. It is known that serum TSH levels are higher in obese individuals. Increased accumulation of fat in the body leads to disruption of the hypothalamic-pituitary-thyroid axis and various disorders of thyroid function.[22,23] In obesity, increased expression of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6 inhibits sodium-iodine mRNA expression and iodine uptake in thyrocytes, leading toa reversible increase in TSH. In our study, the values of glucose, insulin, TSH, ALT, and HOMA-IR did not differ significantly between the patient and the control groups. Metabolic syndrome, animportant public health problem, is considered to be a combination of metabolic abnormalities such as abdominal obesity, hypertension, hyperglycaemia, low-density lipoprotein cholesterol (HDL-C), and high triglycerides.[24] Numerous studies have shown that metabolic syndrome is associated with ERD.[25,26] Some studies have reported that abdominal obesity, the main component of metabolic syndrome, may be a stronger predictor for ERD than obesity. A study conducted by Hsieh et al.[27] in Taiwan to examined the effect of metabolic syndrome components on ERD and they found that there was a linear relationship between the number of metabolic syndrome components and the severity of ERD. The results of the present study are consistent with previous studies that found a significant association between hypertension and ERD.[28,29] In our study, the presence of hypertension was statistically significant in ERD group compared to NERD and control groups. The majority of hypertensive patients in the ERD group were using angiotensin-converting enzyme inhibitors. The high rate of hypertension in the ERD group was associated with visceral adiposity, which is a risk factor for both diseases, rather than a cause-and-effect relationship.

Many studies have suggested that an increased BMI increases thesymptoms of GERD or the risk of development of ERD.[25,30,31] Fujikawa et al.[32] reported a significant relationship between increased BMI and GERD symptoms in patients with NAFLD. In a cohort study of 6215 individuals with GERD conducted by Nocon et al.[33] they examined the effects of BMI on reflux symptoms, frequency, and severity of esophagitis and showed that higher BMI was associated with frequency and severity ofreflux symptoms and an increase in the frequency of esophagitis. Ayazi et al.[34] evaluated 1659 patients with 24-hour pH monitoring and manometer between 1998 and 2008, divided them into four groups based on their BMI values, and assessed their LES pressure and oesophageal acid exposure. In their comparison, increased BMI showed a positive correlation with increased oesophageal acid exposure, and patients with higher BMI were found to have a higher prevalence of defective LES.The likelihood of having a mechanically defective LES was more than twice as high in obese patients compared to normal-weight patients. Our study, no significant difference in BMI values was found between all groups.

In a study of 265 Japanese male with metabolic syndrome conducted by Sogabe et al.[35] it was shown that the risk of developing ERD was higher in individuals with highvisceral fat than those with more subcutaneous fat tissue. In their study, individuals with metabolic syndrome without symptoms of reflux or dyspepsia underwent ultrasonography,

visceral and subcutaneous fat tissues were determined and then upper gastrointestinal endoscopy was performed. It has been reported that the frequency of ERDis higher in these individuals with metabolic syndrome, which is consistent with the literature. Several studies have demonstrated the association between visceral adiposity and increased risk of erosive esophagitis, using expensive imaging modalities such as CT, MRI, and ultrasound to assess visceral fat percentages.

Ze et al.[28] performed endoscopy, blood analysis of metabolic parameters, measurement of waist circumference and CT to examine fat distribution in 728 patients over the age of 40 and reported that patients with ERD had a significantly higher visceral to subcutaneous fat ratio. In a study conducted by Nurleili et al.[18] to determine the difference in visceral fat between patients with ERD and NERD. The gastroesophageal reflux disease questionnaire (GERDQ) was administered to patients, upper gastrointestinal endoscopy was performed in 56 patients diagnosed with reflux based on the questionnaire, and their visceral fat ratio was examined by ultrasonography. ERD was found in 54% of the patients, and it was reported that 64% of these patients were men. As a result of the study, visceral fat thickness measurements did not differ significantly between the NERD and ERD groups. However, it was reported that the severity of esophagitis tended to increase with increasing visceral fat thickness.

Visceral adipose tissue is a source of inflammatory cytokines and is associated with systemic inflammation in obese individuals. Both subcutaneous and visceral fat are considered major features of the metabolic syndrome, and in particularly an excessive accumulation of visceral fat releases several bioactive substances known as adipokines, including TNF-a, resistin, leptin, and adiponectin. These mediators may affect the stomachand/or esophagogastric junction. It has been reported that pro-inflammatory cytokines, such as IL-1 and TNFα, stimulate gastrin secretion around the gastric antrum.[36] Thus, pro-inflammatory mediators such as adipokines can exacerbate or maintainlocal inflammation in the esophagogastric junction afterpathological exposure to oesophageal acid.[35] In addition, obesity is known to be associated with an increased frequency of tLESR and increased acid exposure.[37] However, the underlying metabolic mechanisms and whether other factors play a role in the pathogenesis of erosive esophagitis associated with obesity remain unclear. In our study, higher values of visceral fat percentage, FFM, and muscle mass were found in the ERD group compared with the NERD and control groups. The reason for the high values of FFM and muscle mass in the ERD group is that most of the patients in this group are male. Our study is important in terms of demonstrates the association between visceral adiposity and ERD, regardless of an increase in body fat composition.

This is the first study to assess the relationship between ERD and visceral fat percentage using Tanita, a quantitative, easy-to-use and person-independent method. The present results can contribute to the literature by showing the relationship between adipose tissue and body fat composition studied in the physiopathology of many diseases such as GERD and ERD, which are contemporary disease groups. In patients with GERD complications in our study, Tanita, a method that supports lifestyle changes, which is the first step of treatment, can be used in routine clinical practise and may guide future studies.

CONCLUSION

When the ERD group was compared with the NERD and the control groups, it was found that visceral adiposity was significantly higher in the ERD group. There was no significant difference between the NERD and the control groups. This suggested that visceral adiposity may be a risk factor for ERD. Despite similar mean BMI values across all groups, the statistically significant presence of visceral adiposity in the ERD group suggests that visceral adiposity is a more serious problem than obesity.When comparing the ERD and NERD groups except for the control group, it was found that the majority of patients in the ERD group were male and smokers. Our study confirmed that male gender, smoking, and metabolic syndrome increase the risk of ERD, as has been previously established. A limitation of our study was the high number of smokers in the ERD group. A noteworthy aspect of our study is that this is the first study to assess the relationship between ERD and visceral fat percentage using Tanita in the literature.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Clinical Researches Ethics Committee (Date: 26.02.2019, Decision No: 03/04).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review

A look at common gastrointestinal system diseases: current review

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ABSTRACT

The gastrointestinal system consists of the esophagus, stomach, small intestine, large intestine, and rectum. Although they are called accessory organs, the liver, pancreas, and gallbladder are also evaluated in this system with their vital features. Gastrointestinal system disorders (GISD) are observed quite frequently in society. Considering the morbidity and mortality they cause, effective treatment methods become crucial. Situations such as patients' non-compliance with nutritional recommendations and the inadequacy of pharmacological and surgical methods at some points make different perspectives and treatment methods more valuable. From this point of view, we will try to examine the GISD that causes muscle loss and the physiotherapy modalities that can be applied to these patients in light of the current literature.

Keywords: Gastrointestinal system, physiotherapy, role

INTRODUCTION

The gastrointestinal system (GIS) consists of the esophagus, stomach, small intestine, large intestine, and rectum. Although they are called accessory organs, the liver, pancreas, and gallbladder are also evaluated in this system with their vital features. Gastrointestinal system disorders (GISD) are observed quite frequently in society. Considering the morbidity and mortality they cause, effective treatment methods become crucial. Situations such as patients' non-compliance with nutritional recommendations and the inadequacy of pharmacological and surgical methods at some points make different perspectives and treatment methods more valuable. From this point of view, we will report mostly seen GIS diseses in short.[1-3]

PROTEIN LOSING ENTEROPATHIES

Protein-losing enteropathy (PLE) is a clinical condition that develops as a result of excessive protein loss from the gastrointestinal tract, characterized by low protein in the blood, edema, and fluid accumulation in the lung and heart membranes in some patients. However, to use the term PLE, first, long-term malnutrition, urinary protein loss, and protein production disorders due to liver diseases must be excluded.[1]

Under normal conditions, the contribution of the intestinal mucosa to protein degradation is quite insignificant. However, this rate increases considerably in PLE. The human body can compensate for low protein losses by increasing protein synthesis activities, but when the intestinal loss rate reaches 60%, it is insufficient.[2] Many diseases can cause this clinical condition. From this point of view, it would be more logical to briefly talk about the pathophysiological mechanisms of intestinal-induced protein loss, rather than listing individual diseases.[1,3]

Injury of the intestinal surface and secretion of inflammatory fluid with high protein content due to causes such as inflammatory bowel diseases, infective agents, cancers. Conditions where only permeability increases without erosion or ulceration on the mucosal surface, such as Giardia infection, rheumatic diseases, celiac disease, hypertrophic gastric mucosa. Obstruction of protein-carrying intestinal lymphatics due to either congenital defects or causes such as cancers, granulomatous diseases, and heart failure.[3,4]

Some diseases may cause PLE through several of the above-mentioned mechanisms. Considering that PLE is the result, not the cause, the clinical findings will vary depending on the underlying disease. For example, a factor such as C. Difficile will apply to the hospital with abdominal pain, bloody diarrhea, and fever, while a patient with heart failure will present with shortness of breath and decreased effort capacity. On the other hand, a patient with a decreased circulating immunoglobulin level will have frequent infections. The decrease in the amount of protein will reduce the intravascular oncotic pressure, which will cause fluid leakage from the intravascular to the outside. Fluid accumulation in the intercellular space will appear as edema. Although edema is expected in all patients, it is not that common.[4]

So, are there any laboratory tests to support our diagnosis of suspected patients? Undoubtedly yes. Serum albumin, immunoglobulin, cholesterol, and transferrin levels may be low. In addition, alpha-1 antitrypsin molecules synthesized in the liver can be used for diagnostic purposes. This molecule is excreted in a certain amount with feces under normal conditions and is resistant to digestion. If 24-hour alpha-1 antitrypsin clearance is calculated in the collected stool and

found to be higher than the expected level, this indicates an intestinal-mediated loss. Labeled macromolecules can also be used for this purpose.[5]

After concluding that the patient has PLE, a more detailed examination should be performed for the underlying cause. Although it varies according to the physician's opinion and experience; kidney and liver function tests, celiac disease serology, stool parasite, and microscopic examination, C. difficile toxin in stool, serum vitamin D, and cholesterol level are the recommended tests. In addition; Abdominal imaging methods can be performed for inflammatory bowel diseases, lymphoma, enlargement, and obstruction of the lymphatics. Endoscopic methods that allow direct visualization of the mucosa and obtaining pathological samples may also be preferred. Echocardiography in patients with suspected heart disease, and specific antibodies in rheumatic diseases are other tests that can be preferred.[5-7]

After the diagnosis of PLE is confirmed, the patient's nutrition should be regulated without losing time. Studies support a diet low in fat, rich in protein, and medium-chain fatty acids. Long-chain fatty acids should be avoided. Because these molecules, unlike medium-chain fatty acids, are absorbed through protein. In these patients, diets containing 3 g of protein per kilogram should be preferred. In addition, research should be continued to detect the underlying disease and treatment should be started for it.[7]

INFLAMMATORY BOWEL DISEASES

Inflammatory bowel diseases (IBD) are thought to develop as a result of the impaired immune response against intestinal microflora and include ulcerative colitis (UC) and Crohn's disease (CD).[8] UC is limited to the colonic mucosa, progresses with recurrent attacks, starts from the rectum, and spreads proximally. CD affects the entire gastrointestinal tract from the mouth to the anus. In both diseases, systems such as eyes, joints, and skin may also be affected, as well as intestinal involvement. Its incidence is approximately 12/100,000. Both diseases peak twice, at young and advanced ages. UC mostly affects men and CD affects women more.[9] The probability of having IBD in first-degree relatives of patients has increased approximately thirty times compared to the general population. Likewise, considering that this rate is as high as 35% in homozygous twins, it is obvious that the disease has a serious genetic predisposition.[10] How IBD develops is still unknown. However, in individuals with genetic predisposition, an exaggerated immune response against intestinal flora with the effect of environmental factors is one of the most plausible views. Inadequate intake of breast milk, smoking, excessive consumption of animal foods, and a diet poor in omega-3 fatty acids are the environmental factors that are blamed.[11] With the increase in intestinal permeability, the emergence of an immune response against antigens that cannot pass the mucosal barrier under normal conditions is another mechanism that is held responsible for the development process of the disease. In addition, studies have shown that the balance between Th1 and Th2 cells, which are vital in controlling inflammation, is impaired in these patients.[11-13]

UC begins in the rectum and spreads proximally. Involvement is limited to the mucosa. Areas without involvement are not observed between the intestinal segments. The rectum region is most affected, but the entire large intestine may be affected in one-sixth of patients. Patients usually present with abdominal pain, bloody-mucous diarrhea, and weight loss. These symptoms are often observed as intermittent exacerbations or may be less persistent. One-twentieth of the patients may experience 20-30 defecations per day, fever, and abdominal pain in the form of cramps. There are no physical examination findings specific to UC. During the attack periods, abdominal tenderness and fever are observed. Rectal examination reveals fresh bleeding or bloody stools.[12] In the blood tests performed during this period, an increase in the erythrocyte sedimentation rate, C-reactive protein level and white blood cell level, and anemia may be observed. To exclude other causes, stool culture should be performed together with stool microscopic and parasitological examination. Undoubtedly, endoscopic imaging methods are very valuable in IBD, as they allow both direct visualizations of lesions and biopsy in terms of differential diagnosis. In periods of exacerbation, the mucosa is edematous and prone to bleeding; ulcers and false polyp structures are detected in the intestine. As the disease progresses, the large intestinal mucosa acquires a granular appearance. Contrast-enhanced radiological examinations show a sawtooth appearance in the exacerbation period and a lead pipe appearance in the chronic period. Undesirable bowel-related conditions such as severe bleeding, toxic megacolon, perforation, and obstruction may develop due to UC.[13] In addition, extra-intestinal clinical manifestations such as uveitis, iridocyclitis, pyoderma gangrenosum, erythema nodosum, and ankylosing spondylitis may accompany.[14] In these patients, the probability of developing colon cancer in ten years is one in twenty. In addition, progressive fibrosis of the biliary tract is another feared clinical condition.

The CD is mostly located in the small intestine, the large intestine is less affected. In about half of the cases, both organs are involved. Especially the last part of the ileum is affected in almost all patients. Unlike UC, it first starts with superficial ulcers, then these ulcers merge, but there are intact mucosal areas in between. Because of this segmentary involvement, a cobblestone appearance occurs in the mucosa. Due to the complete involvement of the intestinal wall, thickening of the adjacent mesentery tissue and enlargement of the lymph nodes are observed. Granulomatous inflammation is one of the hallmarks of CD. Fistulas may develop between adjacent bowel segments and between the bowel and other organs and skin. Unlike UC, bloody stools are not expected. Patients mostly present with abdominal pain, fever, and diarrhea. In laboratory examination, an increase in acute phase reactants, increased fat excretion in the stool due to malabsorption, and iron, zinc, and vitamin deficiencies can be detected. In imaging studies, narrowing of the intestinal lumen, wall thickening, fistulas, and abscesses can be observed. Aphthous ulcers are detected in the endoscopic examination and the diagnosis is confirmed by the pathological samples taken. Unlike UC, it progresses with granulomatous inflammation. Abscess, obstruction, fistula, and perforation may develop due to CD.[12,13,15]

In both diseases, diet is primarily regulated. Fluid, mineral, and vitamin supplements are provided. Raw fruits and vegetables, spicy and fatty foods are avoided in the diet. Antidiarrheal and antispasmodic drugs, antibiotics for CH can be used. 5-aminosalicylic acid derivatives, steroids, and classical treatment agents that suppress the immune system are widely used in the treatment. In addition, target-specific monoclonal antibodies have recently been used.[13,16]

LIVER DISEASES

Non-alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is used to express fatty liver. However, secondary causes of fatty liver such as alcohol use should be excluded. The concept of non-alcoholic fatty liver disease (NAFLD) is used only for patients with fatty liver, and the concept of non-alcoholic steatohepatitis (NASH) is used more for conditions accompanied by inflammation. It is the most common liver disease, especially in developed societies and often accompanies diabetes, obesity, hyperlipidemia, and metabolic syndrome. Although its distribution and prevalence vary in different studies, it is thought to affect approximately one-fifth of the population.[17,18]

Unfortunately, the development process of the disease has not been fully elucidated. However, the most accepted theory is insulin resistance. The presence of metabolic syndrome in most of the patients supports this opinion. Fat accumulation occurs in the liver because of excessive absorption of free fatty acids, increased destruction in surrounding tissues, decreased intracellular use, and increased conversion of other nutrients to fatty acids. Insulin resistance lies at the root of these events. Free radicals are formed because of the peroxidation of these accumulated oils. These radicals are reduced through vitamin C, vitamin E, and glutathione, which are among the treatment methods. However, exceeding the capacity causes liver damage. Fatty liver is also observed in hemochromatosis disease, which occurs because of a genetic disorder and is characterized by iron accumulation in the body. Based on this, it is thought that iron has a role in the etiology of NAFLD. In addition, a relationship between NASH and resistance to leptin molecules produced in adipose tissue in the central nervous system has been demonstrated. There is an inverse relationship between the level of adiponectin, another molecule released from adipose tissue, and fatty liver. The opinion that intestinal flora triggers fatty liver and fibrosis in some patients is extremely interesting. Recent studies support this theory. Stellate cells in the perisinusoidal area are responsible for the fibrosis that occurs in the advanced stages of the disease.[13,18-20]

Despite being so common and having serious consequences, its clinical manifestations are rather faint. Complaints are often attributed to other causes, such as weakness, malaise, and discomfort in the upper abdomen. Patients are usually detected incidentally in tests performed for other reasons, and a mild liver enlargement may be observed in approximately one-fifth of them. Laboratory investigations may reveal moderate elevation of transaminases. However, there is no correlation between elevated transaminase levels and liver inflammation. Likewise, a normal range of transaminase levels does not exclude inflammation.[20-22]

For diagnosis, fatty liver should be demonstrated by biopsy or imaging methods, alcohol use and other genetic and viral chronic liver diseases should be excluded. NASH and NAFLD can only be distinguished by pathological examination, but since biopsy is risky and the treatment approach does not change much, this option should be reserved for risky patients only. Patients with signs and symptoms of cirrhosis, high serum ferritin levels, and patients with metabolic syndrome over 45 years of age are likely candidates for biopsy. Detection of more than 5% fat in cells in the biopsy is sufficient for the diagnosis of NAFLD. When this is accompanied by liver cell destruction and fibrosis, the term NASH is used. If inflammation and fibrosis cannot be prevented, liver cirrhosis will be inevitable.[20-23]

Many agents have been tried in the treatment, but the desired results have not been achieved. The only method that is accepted as effective is to achieve weight loss. Weight loss of 0.5-1 kg per week is ideal.[22] In addition, patients should be vaccinated against viral hepatitis. Patients should avoid excessive alcohol consumption. Patients are mostly lost due to cardiovascular diseases. Therefore, glycemia, blood fat levels, and arterial blood pressure should be kept within the appropriate range. Many different drugs, from anti-diabetic agents to statins, have been tried in these patients, but it has been concluded that only Vitamin E and omega-3 fatty acids may be of limited benefit.[23] Therefore, alternative treatment methods are important.

Chronic Viral Hepatitis

The term hepatitis is used to describe inflammation of the liver. It can develop due to bacterial, viral, and parasitic infections, as well as secondary to alcohol use, drugs, and metabolic diseases. Viral agents such as hepatitis A, B, C, E, D, EBV, and CMV can cause liver damage. However, in this section, when we consider the prevalence, we will mention the factors of chronic viral hepatitis (CVH), namely Hepatitis B, C and D. Chronic hepatitis is a definition used for conditions where inflammation in the liver lasts longer than six months. Effective treatment is very important in CVH because it causes cirrhosis and liver cancer in the long term and creates a reservoir for transmission. It is thought that around half a billion people worldwide suffer from CVH.[24]

All three factors are transmitted by blood, sexual intercourse, and from mother to baby during pregnancy through the placenta. Hepatitis C and D virus is RNA virus, hepatitis B is DNA virus. In those who are infected with hepatitis B, the probability of becoming chronic is one in twenty. It is almost inevitable in newborns who pass through the placenta if they are left untreated. Hepatitis C tends to become chronic at a rate of 65%. After the transmission, there is a period when signs and symptoms are not observed, but the virus is detected by laboratory tests. Then comes the stage characterized by nausea, vomiting, loss of appetite, muscle and joint pain, and weakness. This process is followed by jaundice and a recovery period. On the other hand, very few of the patients diagnosed with CVH show signs and symptoms. They may describe weakness, malaise, and mild pain in the upper abdomen. However, these symptoms are not specific to hepatitis and are often ignored. Tenderness and marginal irregularity may be detected in the liver. Patients are mostly diagnosed because of tests performed for another reason. Rarely, skin rash, arthritis, and renal dysfunction may develop.[24-26]

Approximately one-fifth of patients followed up with chronic hepatitis B develop cirrhosis or liver cancer in the future. The development of liver cancer without cirrhosis distinguishes hepatitis B from other diseases. It is the primary cause of liver cancer. Therefore, annual follow-up with ultrasound and serum α-fetoprotein is recommended for patients older than 45 years of age and with a positive family history of liver cancer.[26-28]

Hepatitis C is almost completely asymptomatic. However, in infected individuals, the disease is most likely to become chronic. One-fifth of these people develop cirrhosis. The incidence of liver cancer after cirrhosis is one in twenty per year.[25,27]

Hepatitis D is a defective virus. It can cause disease only in the presence of a hepatitis B surface antigen. While it can be transmitted simultaneously with hepatitis B, it can affect patients who were previously positive for hepatitis B later. Its course is not different from hepatitis B infection alone. Only, the probability of cirrhosis and liver cancer is six in ten, and the development process is faster. In diagnosis, virus-specific antibodies, liver function tests, viral genome determination, and liver biopsy can be used to determine the differential diagnosis and degree of disease. The main goal of treatment is to reduce the inflammatory process and fibrosis in the liver, thereby preventing cirrhosis and other complications. For this purpose, interferon, immunoglobulin, nucleoside and nucleotide analogs, protease inhibitors, and steroids are used. For protection purposes, it is recommended to vaccinate especially healthcare workers, sex workers, dialysis patients, intravenous drug users, patients with organ transplants, and patients whose immune system is suppressed.[25,28]

Cirrhosis

Cirrhosis is derived from the Latin word cirrus, meaning yellow brown, because of the liver appearance observed at autopsy. It is one of the most feared consequences of long-term liver diseases. Regardless of the underlying cause, progressive fibrosis and regeneration nodules cause the deterioration of the architectural structure of the liver, which is indispensable for its functions. Unfortunately, it is irreversible, except in a few rare cases. It is thought to be responsible for approximately 1% of all deaths.[29] Numerous diseases can cause cirrhosis, either by causing long-term inflammation of the liver or by impairing bile flow. However, chronic viral hepatitis, NAFLD, and alcohol use are the main causes. Genetic disorders of iron and copper metabolism, autoimmune diseases involving the liver parenchyma and biliary tract, infections, and heart diseases can be counted among other causes.[30]

Under normal conditions, the production and destruction activities in the extracellular space continue in a balanced way. However, in inflammatory processes where this balance is removed, molecules that provide communication between the secreted cells stimulate the satellite cells in the perisinusoidal area. These cells also synthesize excessive amounts of collagen and secrete it into the intercellular space. Thus, the sieve-shaped and highly permeable vascular structure of the liver, which provides the relationship between cells and blood, is greatly impaired. In a sense, the communication windows are walled and the blood pressure in the vessel rises. The blood coming from the intestines and to be filtered in the liver accumulates due to congestion and tries to reach the heart by alternative routes. As a result of this, the accumulation of fluid, which we call ascites, occurs between the abdominal membranes, varicose veins occur with the expansion of the vessels between the internal organs, and changes occur in the state of consciousness due to the blood passing to the brain without being cleaned in the liver. This situation, which we are trying to explain simply, is called portal hypertension. The elucidation of these physio pathological mechanisms is very important in terms of providing a horizon for new treatment methods.[30-32]

Patients may present with non-liver-specific complaints such as loss of appetite, weight loss, weakness, and fatigue. Therefore, these patients are often not diagnosed in the early stages of their disease. However, if the disease progresses, more serious conditions such as jaundice, itching, swelling in the abdomen, bleeding from the mouth or anus, and changes in consciousness may occur. Less frequently, women may apply to the hospital with menstrual irregularities and men with impotence.[32] When detailed physical examination is done in patients; jaundice on the skin, reticulated enlargements in the superficial veins,[33] enlargement in the breast can be detected. Abdominal swelling due to fluid accumulation between the abdominal membranes,[34] increase in liver size and irregular margins, enlargement of the spleen, redness of the palm, and changes in nail structure may also be detected.

Laboratory examinations may reveal low hemoglobin, thrombocyte, and albumin levels, prolongation of prothrombin time, and elevated liver enzymes. If ultrasonography, tomography, or magnetic imaging is performed in these patients, nodular structure, marginal irregularity, atrophy, or left-sided hypertrophy can be observed in the liver. In patients with cirrhosis symptoms, if laboratory and imaging findings are supporting this, or if life-threatening complications such as ascites, esophageal variceal bleeding, and liver-related changes in consciousness have developed; biopsy is not necessary for diagnosis. This procedure should be reserved for patients for whom the detailed examination is made for the cause after the diagnosis of cirrhosis, but for which no conclusion can be drawn.[35]

After the diagnosis of the disease is finalized, it is very important to reveal the cause. Because with the interventions to be made, the course of the disease may slow down.[36] However, there are precautions to be taken for all patients. All patients should stay away from alcohol and substances harmful to the liver and be vaccinated against hepatitis B and hepatitis A. Diet and exercises should be regulated and followed, and daily weight measurements should be made. Patients should be advised not to be constipated. They should be followed up with endoscopic imaging for variceal bleeding every two years, and ultrasound and blood tests for liver cancer every six months. Patients should be included in the liver transplant program unless there is a contrary situation in terms of transplantation. However, the high prevalence of the disease, the low number of donors, and the inadequacy of experienced centers prolong the waiting period. In this respect, alternative treatment methods and perspectives are of vital importance for both patients who are not suitable for transplantation and for patients waiting for transplantation.[33-36]

CHRONIC PANCREATITIS

The pancreas is located behind the stomach wall. It acts as the conductor of the metabolism in the digestion and absorbability of food with the enzymes it produces as an exocrine gland and the hormones it secretes as an endocrine gland. Chronic pancreatitis is a process in which the structural integrity of the pancreas is irreversibly impaired due to progressive inflammation and fibrosis and the pancreas cannot perform its functions.[37,38]

Although the incidence varies in societies depending on alcohol consumption habits, it can be said that the annual number of new cases is 3-9/100000. Alcohol, genetic diseases such as cystic fibrosis, conditions that obstruct the pancreatic duct such as stone or tumor, autoimmune diseases, and excessive serum triglyceride levels, may cause chronic pancreatitis. However, although it has been revealed that these diseases are associated with chronic pancreatitis, the development process of the disease is still unknown. One of the hypotheses is that a plug is formed in the pancreatic duct because of a protein-containing secretion that cannot be buffered by secretin and bicarbonate. The presence of patchy inflammatory cells in the autopsy series supports the opinion that immune response occurs in individuals with a genetic predisposition to an unidentified factor or factors, and this process causes long-term damage to the pancreatic tissue. No matter how the process progresses, the unchanging situation is the deterioration and irreversible destruction of the microarchitecture of the organ - as described in cirrhosis - because of increased collagen accumulation in the intercellular space in response to inflammatory cytokines.[38-42]

So, with which complaint do patients apply to the hospital more? -Pain. This pain is localized to the upper midpoint of the abdomen and may radiate to the back. It usually starts 15-30 minutes after meals. It may be accompanied by nausea and vomiting. The patient can relax by sitting and leaning forward. While the pain lasts for a few days in the initial stages of the disease, the pain becomes chronic as the process progresses.[40] Considering that ten percent of healthy tissue is sufficient for the organ to perform its functions, patients may rarely present with pancreatic insufficiency findings. Fatty, foul-smelling stools, weight loss, and deficiency of especially fat-soluble vitamins A, D, E, K, and cobalamin can be observed.[41] Similarly, diabetes may develop because of the destruction of islet cells. Unfortunately, there is no physical examination finding specific to the disease, but tenderness can be detected in the epigastric area.

There is no specific laboratory test that can detect the disease directly. Serum amylase and lipase tests, which are very important in acute pancreatitis, are not very useful in these patients. For this reason, pancreatic ultrasound, tomography, and magnetic imaging can be performed in patients clinically compatible with chronic pancreatitis. Atrophy, duct enlargement, calcification, cyst formation, or anatomical disorder may be observed in the gland. In cases where these examinations are insufficient, endoscopic methods can be tried. In addition, stool fat determination and pancreatic stimulation tests can be performed for malabsorption.[42-44]

Providing pain control is the primary goal in the treatment of the disease. In addition to specific treatment methods for the underlying disease, there are also precautions that all patients must comply with. Smoking and alcohol use should be stopped, and frequent and less nutrition should be provided. A diet rich in medium-chain fatty acids is another method that may be beneficial. In addition, pancreatic enzyme supplements and vitamin preparations can be used. Tricyclic antidepressants, morphine derivatives, and pregabalin can be preferred for pain control. Nerve blockade for the celiac ganglion can be applied in patients who do not benefit. In cases where all these methods are insufficient, surgical methods can be considered.[43,44]

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS), which was called spastic colon in the past and is also known as sensitive intestine today, is a common gastrointestinal disorder characterized by chronic abdominal pain and changes in bowel habits. While its incidence is 10-15% (45-50) in North America, its incidence in Europe is around 11.5%, although it varies from country to country. Although IBS can be seen in all ages and genders, it is more common in young women.[45-52]

The pathophysiology of the disease has not been fully elucidated. Traditionally, gastrointestinal motility and intestinal hypersensitivity have been emphasized. Recent studies focus on the role of inflammation, microbiota, food sensitivity, and genetic predisposition.[45,47,51,52]

IBS patients may present to the hospital with a wide variety of symptoms, both gastrointestinal and non-gastrointestinal. Symptoms such as abdominal bloating, flatulence, belching, gastroesophageal reflux, nausea, dysphagia, and early satiety are common in patients with IBS. Although symptoms related to chronic abdominal pain and changes in bowel habits are not only seen in IBS, but they are also necessary for the diagnosis of IBS.[51-53]

CHRONIC ABDOMINAL PAIN

Abdominal pain is described as a cramping sensation of varying severity that flares up from time to time. The location and character of the pain are very variable. Various factors such as emotional stress, and food consumption can increase the pain, defecation usually provides some relief. This pain does not prevent falling asleep and does not wake up from sleep. Abdominal pain should not be associated with weight loss, rectal bleeding, or anemia and should not be progressive.[47,53,54]

Changes in Bowel Habits:

Patients with IBS present with diarrhea, constipation, both diarrhea, and constipation, or a bowel habit that can turn into diarrhea or constipation without both. Diarrhea usually occurs in the form of small to medium-volume soft stools, at the time of waking up in the morning or after meals. Approximately half of the patients have mucus discharge with feces. Large-volume diarrhea, bloody stools, oily stools, and nocturnal diarrhea are not related to IBS and an underlying organic cause should be investigated. Constipation can last for days or months. Defecation is difficult and patients may not feel complete relief after defecation, even if the rectum is empty.[52-54]

IBS is divided into 4 subgroups according to changes in bowel habits.[54,55]

i. IBS with diarrhea
ii. IBS with constipation
iii. Mixed type IBS
iv. Unclassifiable IBS

There is no biological marker or imaging method for the diagnosis of IBS. Considering the symptoms, it was tried to establish standard criteria for diagnosis and the Rome IV diagnostic criteria, which were renewed in 2016, came into use. According to this; diagnostic criteria were defined as the presence of abdominal pain that started at least six

months ago and recurring at least once a week in the last three months, along with two or more of the following three criteria.[55]

i. Relief with defecation
ii. Accompanied by a change in stool frequency
iii. With a change in stool shape

Tests to diagnose the disease should be limited. Further investigation is not recommended if there are no alarm symptoms and the diagnostic criteria for IBS are met. Many conditions such as inflammatory bowel disease, celiac disease, lactose intolerance, fructose intolerance, and microscopic colitis can be confused with IBS because they have symptoms like IBS. Further imaging studies and/or endoscopic examination may be required in patients with alarm symptoms.[53-55]

Since the pathophysiology of the disease is not fully understood, there is no effective treatment method. In the treatment of all patients with IBS, it is important to first establish a reliable doctor-patient relationship. Lifestyle changes and dietary adjustments are recommended for mild IBS patients whose quality of life is not impaired. It is recommended not to consume gas-inducing foods (beans, onions, cabbage, raisins, bananas, apricots…), alcohol, and caffeine. A low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet is recommended. Fiber consumption is recommended in IBS patients with constipation. In moderate and severe IBS patients, symptomatic pharmacological agents are used for the most severe complaints of the patients. These agents can be listed as antidiarrheal drugs, bile acid sequestrants, 5-HT3 receptor antagonists, osmotic laxatives, lubiprostone, spasmolytic agents, antidepressants, antibiotics, and probiotics.[51,53-55]

CONCLUSION

In this review we shortly reported the most common causes of GIS diseases in terms of clinical findings and mostly used treatment modalities. Other aspects of treamentent modalities are in development process and we believe that they will provide many opportunities to clinicans and patients.

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Letter to the Editor

Evaluation of hematological indices in patients with colon cancer

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Dear Editor,

I read with interest the formerly published paper entitled "Retrospective evaluation of platelet indices and RAS mutations in patients with colon cancer" by Şanlıer et al.[1] In that published paper, the authors evaluated the hematological indices in colon cancer patients and their relationships between RAS mutations. It has been noticed that the authors evaluated neutrophil to lymphocyte ratio (NLR), mean platelet volume (MPV), platelet to lymphocyte ratio (PLR) and red cell distribution width (RDW) as hematological indices in colon cancer cases. I would like to thank the authors for valuable contribution to the literature for especially topic on colon cancer.

Neutrophil to lymphocyte ratio is an old biochemical parameter that is often used as an indicator of inflammation, but has recently been used eagerly by many researchers.[2] The fact that it is cheap and easy to obtain has caused this parameter to be used frequently in scientific studies. Previously, it has been shown that hepatitis B and/or C infection, diabetes mellitus disease, many kind of heart diseases, thyroid functional abnormalities, many kind of drugs and medications, many kind of infections and inflammatory diseases (acute pancreatitis etc), many kind of malignancies (such as esophageal cancer, lung cancer etc) may easily affect the hematological biomarker NLR.[2-7] In line with these facts, it would have been more better if Şanlıer et al.[1] had mentioned these NLR-affecting disease while evaluating the NLR in colon cancer. On the other hand, if they added more patients to the study, the results would be stronger and more objective. Moreover, it would be more relevant if the researchers had mentioned the time elapsed between obtaining the blood samples and measuring this parameter, because waiting time period may easily affect NLR.[3,5-7]

Mean platelet volume is also an easily available and a cost-effective biochemical parameter that used currently in many wide spectrum studies. It has been shown that, besides colon cancer and many other types of cancers, hepatitis B and C infection, several bacterial and viral infections, autoimmune disorders, thyroid diseases, chronic renal failure, a lot of inflammatory status may also affect MPV levels.[8-12] It would have been better if the authors stated these all mentioned MPV affecting conditions above while determining the role of MPV in colon cancer cases. Again, blood sample collecting time and MPV testing time is important for securing an optimal and correct MPV value.[9-12]

Platelet to lymphocyte ratio[4,5] and platelet distribution width (PDW) are also platelet based biochemical markers which are used in Şanlıer et al.[1] study. As mentioned above, these two platelet based easily available markers are also affected many kind of chronic diseases disease, malignities and also inflammatory conditions.[4,5,13,14] Again, it would have been more relevant if these situations were taken into consideration while predicting the relationship between RAS, colon cancer and these biomarkers.

CONCLUSION

I believe that the results, finding and statements of Şanlıer et al.[1] will lead and facilitate to newer valuable studies focusing on relationship between PLR, PDW, NLR, MPV, RDW, and colon malignities. But, it should not be overlooked that these hematological indices may not be true indicators of colon malignities related conditions without a clear and detailed exclusion criteria. Moreover, disease associated other clinical, laboratory, and imaging variables should be taken in to consideration.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

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