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Original Article

The Effect of Hot Pepper, Sumac, and Chewing on Gastric inhibitory peptide, Glucagon-like Peptide, and Cholecystokinin Hormone Secretion

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ABSTRACT

Background: The influence of various dietary factors on metabolic responses and gastrointestinal function has been the subject of extensive research. In this study, we aimed to investigate the effects of capsaicin, chewing, and sumac on metabolic parameters and gastrointestinal function in healthy male volunteers.

Methods: A total of 33 healthy male volunteers aged 18 to 40 years were recruited for the study. Participants underwent four different experimental groups: capsaicin (n=10, a mixed meal containing 467 kcal [22% protein, 46% fat, 32% carbohydrates] and 1 g of capsaicin), chewing (n=11, chewed sugar-free and non-artificial sweetener gum for 5 minutes), sumac (n=7, a meal containing a total of 328 kcal [28% fat, 63% carbohydrates, 9% protein] and 2 g of sumac, and sumac with defecation groups (n=10, a meal containing a total of 328 kcal [28% fat, 63% carbohydrates, 9% protein] and 2 g of sumac. Metabolic parameters including glucose, insulin, Glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and cholecystokinin (CCK) levels were measured from blood at 0, 5, 10, 25, 45, 60, 120, and 180 minutes following digestion. Gastrointestinal function was assessed by monitoring bowel movements, stool consistency, and appetite levels. $p<0.05$ was assumed statistically significant.

Results: The addition of capsaicin did not result in significant changes in glucose, insulin, GIP, GLP-1, and CCK levels, as well as appetite and energy intake. Chewing sugar-free gum also had no significant effects on the examined parameters. Similarly, the consumption of sumac did not lead to significant alterations in glucose, insulin, GIP, GLP-1, and CCK levels, appetite, or energy intake. However, it was observed that sumac consumption for one week resulted in looser stools without affecting bowel movement frequency or appetite.

Conclusion: Our findings suggest that chewing or the inclusion of capsaicin, or sumac in the diet does not exert significant effects on metabolic parameters and appetite in healthy male volunteers. However, sumac consumption over a one-week period was associated with a change in stool consistency. Further investigations are required to elucidate the underlying mechanisms responsible for the observed effects and to explore the potential long-term implications of these dietary factors on metabolic and gastrointestinal health.

Keywords: Capsaicin, chewing, cumac, gastrointestinal function, metabolic parameters

INTRODUCTION

Nutrition is essential for maintaining a healthy lifestyle. The central centers regulating feeding behavior are located in the brain, particularly in the hypothalamus and its surroundings (1). Signals from adipose tissue, the gastrointestinal system, and other organs involved in metabolic events reach the central nervous system through neural and humoral mediators. Necessary adjustments are made, and then these signals are transmitted to the periphery through neural, endocrine,

and paracrine mediators (2).

Several hormones play a role in appetite regulation, including cholecystokinin (CCK), gastrin, ghrelin, gastric inhibitor peptide (GIP), glucagon-like peptide-1 (GLP-1), GLP-2, motilin, oxyntomodulin, postprandial insulin and hyperglycemia (PHI/PHV), pancreatic polypeptide (PP), peptide YY3-36 (PPY3-36), secretin, somatostatin, leptin, bombesin, gastrin-releasing peptide (GRP), and apolipoprotein A/V (APO-A/V) (3-6). Among these hormones, GIP is closely related to fat metabolism (7). Although the mechanisms of GIP secretion are not fully understood, various studies have observed that it is influenced by the type of meal and the composition of consumed fats (7,8). It is thought that sensory afferent nerves of the intestine and enteroendocrine cells play a role in this secretion (9).

The fact that GIP secretion starts to increase immediately after a meal (5-15 minutes) suggests that central mechanisms may also play a role in the control of hormone secretion (10). GIP is also present in saliva, and the amount of GIP in saliva decreases after meals (10). Chewing is probably decreasing GIP levels (11). Postprandial plasma levels of CCK can vary depending on the content of the food consumed. While both CCK and GLP-1 are involved in appetite regulation and satiety, their interactions and potential effects on each other are still being studied, and the precise relationship between postprandial CCK levels and GLP-1 remains unclear (12).

Capsaicin is one of the main components of chili pepper (13). Thousands of transient receptor.potential vanilloid-1(TRPV1; capsaicin receptor) receptors are found on sensory nerves. Capsaicin activates the TRPV1 channel, which is predominantly expressed in sensory neurons. Activation of the TRPV1 channel leads to the influx of calcium ions (Ca2+) into the sensory nerve cells, resulting in depolarization and the generation of action potentials. However, the exact action of capsaicin on gastrointestinal motility is unclear (14,15).
Capsaicin increases blood flow in the gastrointestinal system. Its effects on fat absorption and energy are believed to occur through sympathetic activity. It has been shown that it has a positive effect on appetite and fat metabolism (16,17). It is thought that dietary chili pepper supplementation or using it as a food additive with an ideal dosage may be a tentative method for capsaicin to play its protective roles in metabolic health (18). Smeets et al. reported that an acute lunch containing capsaicin had no effect on satiety, energy expenditure, and peptide YY but increased GLP-1 and tended to decrease ghrelin (18). GIP, which is highly likely to undergo changes in its blood levels due to capsaicin administration, was not studied in these experiments.

Another spice that is expected to alter peptide hormones secreted from the intestine is sumac. It has been shown that sumac extracts lower blood sugar levels in humans and inhibit carbohydrate digestion enzymes such as amylase and alpha-glucosidase in vitro environments (19,20). It has been demonstrated that inhibitors of amylase and alpha-glucosidase, when given with or before a meal, increase GLP-1 levels and decrease GIP levels (21,22). Whether sumac has a similar effect is not yet known.

This study aims to investigate the effects of capsaicin, chewing, and sumac on metabolic parameters and gastrointestinal function in healthy volunteers by examining the influence of these dietary factors on various metabolic parameters such as glucose, insulin, GLP-1, GIP, and CCK levels. We also aim to assess the impact of capsaicin, chewing, and sumac on gastrointestinal function, including bowel movements, stool consistency, and appetite levels.

METHODS

Participants and Study Design

A total of 35 volunteers enrolled in the study. Twenty-five individuals were involved in peptide measurements, while 10 individuals were involved in stool characterization. Volunteers were recruited by posting advertisements explaining the experiment and its purpose at the Marmara University Faculty of Medicine Hospital. Those who responded to the advertisements were interviewed face-to-face, provided with detailed information, and enrolled in the study after giving written consent. The study received approval from the Marmara University Ethics Committee in June 2009 (Ethics Committee decision no. MAR-Y4-2009-0226, dated June 5, 2009). One participant who was involved in the chewing experiments was excluded from the study because they were diagnosed with type 2 diabetes. Another participant did not attend the experiments in the second week, so their data were not used. The total number of completed participants in the study is 33.
All participants' height.and.weight were measured, and their body mass index(BMI) was calculated (BMI = Body Weight (kg) / Height (m)²). Individuals with a BMI between 20-25 kg/m² were considered to have a normal weight, those with a BMI between 25-30 kg/m² were considered overweight, and those with a BMI above 30 kg/m² were considered obese.

Inclusion criteria: Healthy male volunteers between the ages of 18-40 without any known illnesses were included in the study.

Exclusion criteria: Individuals who have consumed water within the past 2 hours or have chewed gum, individuals who have smoked within the past 12 hours, individuals who have taken any medication within the past week, individuals who have had a febrile illness within the past week, individuals who have attempted

to follow any diet program within the past month, individuals who have experienced a weight change of more than 5% in the past 3 months, individuals with a BMI over 30 for meal-based studies, individuals who have consumed more than 210 grams of alcohol per week, and individuals with systemic illnesses.

Experimental Groups

Capsaicin group (n=10): A meal containing a total of 467 kcal was given. The meal consisted of 100 g of eggs, 10 g of butter, 30 g of low-fat cheese, and 70 g of white bread, with a composition of 22% protein, 46% fat, and 32% carbohydrates. The participants were given the meal with or without the addition of 1 g of capsaicin, with at least a one-week interval between the two conditions. Blood samples were taken at 0-5-10-25-45-60-120 and 180 minutes after the meal. Four hours after the meal, all participants were allowed to eat until they were full at a buffet, and the amount and type of food consumed were recorded. The participants' hunger and satiety levels were recorded using a visual scale before and after each meal. The Capsaicin content of the red pepper ingested with the meal was determined by a High-Performance Thin Layer Chromatography (E Yeşilada) using methanolic extracts at Yeditepe University Faculty of Pharmacy.

Chewing group (n=11): Participants chewed sugar-free and non-sweetened FALIM gum for 5 minutes. Blood samples were taken at 0-5-10-25-45 and 60 minutes after chewing. One participant was excluded from the study due to a new diagnosis of diabetes.

Sumac group (n=7): A meal containing a total of 328 kcal was given. The meal consisted of 350 g of potatoes, 10 g of olive oil, and unsweetened tea, with a composition of 28% fat, 63% carbohydrates, and 9% protein. The participants were given the meal with or without the addition of 2 g of sumac, with a one-week interval between the two conditions. Blood samples were taken at 0,10,30,60,90,120, and 150 minutes after the meal. Three hours after the meal, all participants were asked to eat until they were full at a buffet, and the participants' hunger and satiety levels were evaluated using a visual scale before and after both meals.

Sumac and defecation groups (n=10): Participants were monitored for 15 days regarding their daily number of bowel movements, the type of stool according to the Bristol scale, and their hunger level before the evening meal and their satiety level after the evening meal. During one week, participants were given 2 g of sumac along with a desired meal. The participants' diet was not intervened during this study.

Determination of Hunger and Satiety Levels

Before starting each meal and immediately after finishing, participants were asked to indicate their level of hunger or satiety on a visual scale ranging from 1 to 10, where 0 represented very hungry and 10 represented very full.

Measurement of Energy Intake

In the capsaicin experiments, 4 hours after the initial meal, and in the sumac experiments, 3 hours after the initial meal, participants were provided with food and beverages in a pizzeria in the desired amounts, and all consumed items were recorded. The calorie content and distribution of macronutrients in the consumed meal were calculated using specialized software (Ebispro for Windows, Stuttgart, Germany; Turkish version: BeBiS, Version 6.1) with the assistance of a dietitian. The nutritional content of the food items in the software is derived from the German Food Code and Nutrient Database (Bundeslebensmittelschluessel; BLS) at a 97% rate, with the remaining data obtained from the USDA database.

Blood Sampling and Storage Conditions

Venous blood samples for GIP, CCK, and GLP-1 analysis were obtained from an indwelling venous catheter at specified time points as mentioned above. Aprotinin (AppliChem, Darmstadt, Germany, catalog no: A2132, 6511,52 g/mol, 6000 KIU/mg) was dissolved in physiological saline. Venous blood was collected into chilled tubes containing aprotinin (5000 KIU/ml of blood) and EDTA (1 mg/ml of blood; Merck, Darmstadt, Germany). The tubes were centrifuged at 4°C, and plasma was immediately stored at -20°C until assayed. Blood samples for glucose and insulin analysis were collected into blank tubes, centrifuged at 4°C, and measurements were done immediately.

Peptide determination

CCK, GIP, and GLP-1 measurements were conducted at the University of Copenhagen using the radioimmunoassay (RIA) method. CCK was determined using antibody 92128 in the biochemistry laboratory of the University of Copenhagen (23). GIP and GLP-1 were determined using antibodies R65 and 89390, respectively, in the clinical physiology laboratory of the University of Copenhagen (24).

Plasma concentrations of CCK, GIP, GLP-1, PYY, and PP were all measured by highly specific RIAs: CCK using the antibody 92128 (23), GIP using antibody R65, and GLP-1 using antibody 89390 by methods (24). Insulin concentrations were measured immunometrically (Modular E, Roche Diagnostics, Germany). Measurements were conducted in the clinical physiology laboratory of the University of Copenhagen.

Capsaicin Determination

The Capsaicin content of the red pepper ingested with the meal was determined by High-Performance Thin Layer Chromatography (E Yeşilada) using methanolic extracts at Yeditepe University Faculty of Pharmacy (25)

Insulin and Glucose Determinations

Insulin and glucose levels in the separated serum samples were analyzed immediately at the Marmara Biochemistry Center laboratory. Glucose levels were measured spectrophotometrically using the Roche-Hitachi 917 kit and the Roche Hitachi Modular Analytics device. Insulin was determined using the electrochemiluminescence immunoassay method with the Modular Analytics E170 device and the COBAS kit.

STATISTICAL ANALYSIS

The continuous data were expressed as mean and standard deviation, while categorical data were presented as median and range. Parametric tests were used for normally distributed continuous data, and nonparametric tests were used for non-normally distributed continuous data and categorical data.

In the experiments investigating the effects of sumac, chili pepper, and chewing, the area under the curve (AUC) of insulin, glucose, and peptide levels, obtained by plotting them against time, was calculated using the trapezoidal method. Differences between experimental days were analyzed using paired t-tests. The effect of time on changes in glucose, insulin, and peptide levels was evaluated using one-way ANOVA, while the combined effect of time and treatment was analyzed using two-way ANOVA. Additionally, the values obtained from experiments with and without chili pepper/sumac at each sampling time were compared using paired t-tests. In the sumac and defecation experiments, the daily number of stools and stool patterns for each participant were averaged for weeks with and without sumac, and the means were compared using paired t-tests. P-values less than 0.05 were considered statistically significant.

RESULTS

The number of participants in each experiment and the demographic and anthropometric characteristics of the participants are presented in Table 1.

The Effect of Chili Pepper

a. Effect on Serum Glucose and Insulin Levels

The changes in serum glucose and insulin levels before breakfast and during the following 180 minutes in the chili pepper experiments are summarized in. In the chili pepper experiments, serum glucose was significantly higher at 45 minutes compared to the baseline ($p<0.05$), while no significant increase in serum.glucose.was observed in the experiments without chili pepper. Consumption of chili pepper did not cause any significant differences in serum glucose levels at the time points of blood sampling, and the total area under the.glucose. curve was similar in both the chili pepper and non-chili pepper experiments. When considering the combined effect of time and treatment (two-way ANOVA), it was observed that the changes in glucose levels were time-dependent ($p<0.001$ for time, $p=0.90$ for treatment, and $p=0.99$ for time and treatment) (Figure 1).

Serum insulin levels were significantly higher than the baseline at 25 and 45 minutes in the experiments without chili pepper ($p<0.05$), and at 25, 45, and 60 minutes in the chili pepper experiments ($p<0.01$, $p<0.05$, and $p<0.01$, respectively). There were no significant differences in insulin values at the time points of blood sampling between the experiments, and the area under the insulin curve did not differ between the two experiments (Table 2). When evaluating the combined effect of time and chili pepper (two-way ANOVA), it was found that the changes in insulin levels were only influenced by time ($p<0.0001$ for time, $p=0.55$ for chili pepper, and $p=1$ for time and chili pepper).

b. Effect on Plasma Peptides (GIP, GLP-1, and CCK)

CCK: In the control experiments, plasma CCK levels increased above baseline at 45-180 minutes ($p<0.01$). In the chili pepper experiments, plasma CCK levels increased at 25-180 minutes ($p<0.01$) and remained elevated at 180 minutes ($p<0.05$). There was no significant difference in plasma CCK levels between the time points of blood collection. The area under the CCK curve was similar in both experimental groups. Plasma CCK levels showed a significant time-dependent change, while they were not affected by chili pepper ingestion (Two-way ANOVA, time: $p<0.001$, chili pepper: $p=0.75$, time*chili pepper: $p=0.90$) (Figure 1).

Table 2. Serum glucose and insulin levels in the chili pepper experiments

Time, minute	0	5	10	25	45	60	120	180	AUC†	AUC†
Glucose mg/dl									mg/dl/min	
Capcaicine free	89.60±18.65	88.50±20.17	91±17.8	106.7	105,6±23,9	100±30.5	93.2±22.9	93.8±17.4	96.92±21.89	98.62±23.12
Capcaicine	89.3 ±10.53	87.9 ±9.34	91.8±10.8	105.6±12.36	108.7±19.10	104.2±21.2	89.1±12.8	92.0±8.40	96.35±12.4	99.2±14.6
Insulin mIU/ml									mIU/ml/min	
Capcaicine free	6.98± 4.86	11.55± 9.2	16.78± 9.8	46.65± 63.3	45.69±42.18	43.63±34.46	19.3±14.23	9.1±5.0	26.79± 2.17	
Capcaicine	5.9±2,86	7.0± 4.0		42.9±36.15	35.96± 30.1	44.53± 5.98	14.85±11.2	7.96±4.08	24.17±12.93	

The data, presented as mean ± standard deviation, was analyzed using nonparametric paired t-test. The area under the curve (AUC) was calculated for each participant. † Significant difference compared to baseline ($p<0.05$)

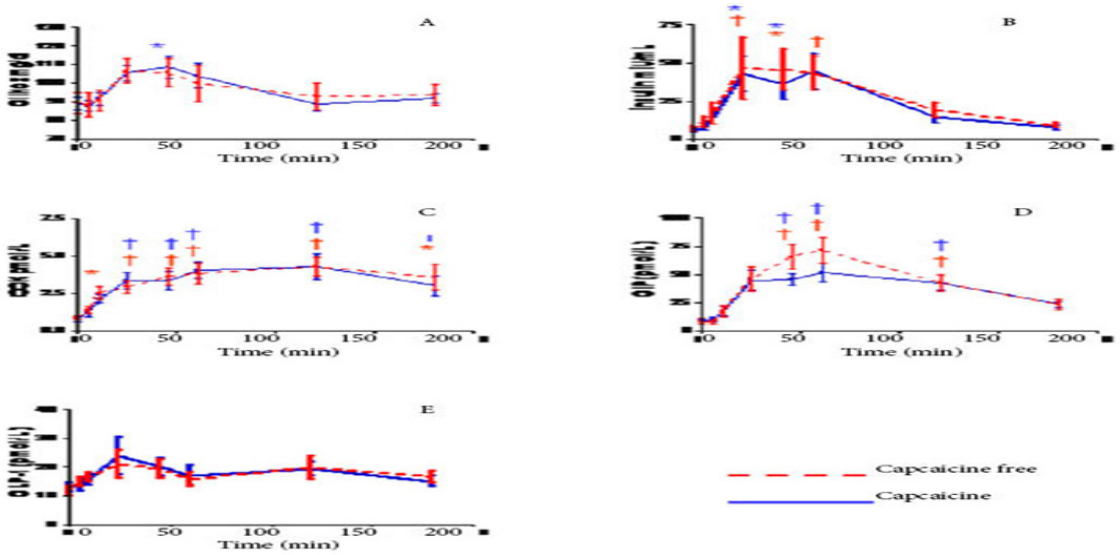

Figure 1. Response of glucose (A), insulin (B), CCK (C), GIP (D), and GLP-1 (E) during a 180-minute period in experiments with spicy pepper (blue solid line) and without spicy pepper (red dashed line), following the consumption of a mixed meal containing 467 kcal (22% protein, 46% fat, 32% carbohydrates). Glucose was significantly higher at 45 minutes in the spicy pepper experiment, while insulin was higher at 25 and 45 minutes in the non-spicy pepper experiment and at 25, 45, and 60 minutes in the spicy pepper experiment compared to baseline. CCK levels were higher at 45-180 minutes in the non-spicy pepper experiments and at 25-180 minutes in the spicy pepper experiments, while GIP response was higher at 45-120 minutes in all experiments compared to baseline. GLP-1 levels did not exceed the baseline. The consumption of spicy pepper did not result in significant changes in the examined parameters. †p<0.01, *p<0.05 compared to baseline.

GIP: In both the control and chili pepper experiments, plasma GIP levels increased above baseline at 25, 45, 60, and 120 minutes. There was no significant difference between the total integrative GIP response and the plasma GIP levels at the examined time points between the two experiments. Plasma GIP levels showed a significant time-dependent change, while they were not affected by chili pepper ingestion (Two-way ANOVA, time; p<0.0001, chili pepper; p=0.128, time*chili pepper; p=0.40) (**Figure 1**).

GLP-1: There was no significant increase in plasma GLP-1 levels compared to the baseline in all experiments. There was no significant difference in GLP-1 levels between the examined time points in the experiments, and the area under.the.curve was similar. The two-way ANOVA test did not show any significant difference related to time or chili pepper ingestion (Two-way ANOVA, time; p=0.22, chili pepper: p=0.30, time*chili pepper; p=0.90) (**Table 3**).

c. Effects on appetite and total energy intake

There were no significant differences in the degree of hunger before breakfast or before lunch between the non-spicy pepper and spicy pepper experiments (**Figure 2**). Similarly, there were no differences in hunger ratings before and after the buffet meal between the experiments. There were no significant differences in total energy intake or the distribution of energy intake according to food groups during the buffet meal.

Effect of Chewing

a. Impact on serum glucose and insulin levels

Chewing sugar-free gum for five minutes did not significantly alter glucose and insulin values at 0, 5, 10, 25, 45, and 60 minutes compared to baseline levels.

b. Influence on plasma peptides (GIP, GLP-1, and CCK)

Table 3. Plasma levels of CCK, GIP, and GLP-1 in chili pepper experiments

Time, minute	0	5	10	25	45	60	120	180	AUC† (0-180)	AUC (0-120)	AUC (0- 75)
CCK pmol/L									pmol/L/min		
Capcaicine free	0.90±0.41	1.37±0.76	2.51±1.39	2.93±1.32	3.60±1.83	3.83±2.26	4.27±1.92	3.59±2.75	3.14±1.92		
Capcaicine	0.83±0.55	1.21±0.88	2.13±0.93	3.35±1.67	3.33±1.92	4.05±1.68	4.27±2.75	3.01±.,01	3.37±1.90		
GIP pmol/L									pmol/L/min		
Capcaicine free	4.50±4.51	7.88±4.83	17.25±14.35	50.00±26.29	69.20±2.,47	71.55±34.88	46.00±19.30	25.16±10.72	43.91±21.50	47.29±23.23	55.33±27.80
Capcaicine	6.55±5.01	8.22±4.71	19.12±11.19	51.33±25.03	48.87±9.59	53.88±21.90	44.10±19.77	23.55±8.06	43.85±19.84	41.02±16.08	48.29±16.63
GLP-1 pmol/L									pmol/L/min		
Capcaicine free	12.38±3.95	14.88±4.62	16.71±4.68	18,16±9.21	15.90±4.30	15.77±7.17	16.25±4.30	14.83±3.81	16.07±5.94	14.76±5.57	
Capcaicine	14.10±5.49	16.11±5.66	17.50±4.75	17.55±4.90	17.42±4.11	16.00±4.92	18.22±6.03	15.11±5.23	15.96±7.24	15.75±3.69	

N=10, the data were expressed as mean±standard deviation and compared using nonparametric paired t-tests. The area under the curve (AUC) was calculated.†

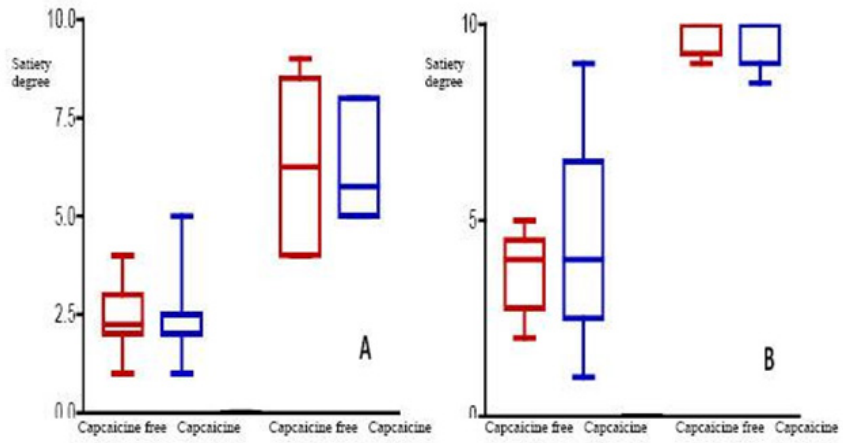

Figure 2. Degree of fullness perceptions before and after (A) breakfast and (B) lunch in the non-spicy pepper (red) and spicy pepper (blue) experiments. Consuming spicy pepper did not significantly alter the feeling of fullness.

Chewing sugar-free gum for five minutes did not result in a significant change in plasma peptide levels at 0, 5, 10, 25, 45, and 60 minutes.

Sumac's Effect

a. Impact on serum glucose and insulin levels

Glucose: Fasting plasma glucose levels were similar between the experiments with and without sumac. The mixed meal significantly increased plasma glucose levels compared to baseline at 30 minutes on both sumac and non-sumac experiment days ($p<0.01$). There was no significant difference in glucose values between the two experimental groups at the time points of blood collection. Similarly, the area under the curves obtained by plotting glucose values over time was similar for both sumac and non-sumac experiment days. In two-way analyses, time significantly influenced glucose levels ($p<0.0001$), while sumac consumption did not have a significant effect ($p=0.35$). When both variables were evaluated together, there was no significant difference between the experiment days ($p=0.66$).

Insulin: Fasting serum insulin levels were similar between the experiments with and without sumac. The mixed meal, whether consumed alone or with sumac, significantly increased serum insulin levels at 30 and 60 minutes compared to baseline ($p<0.01$). There was no significant difference in insulin measurements between the experiments at the time points of blood collection.

The area under the curve obtained by plotting insulin values over time did not differ between the experiments with and without sumac. When time and sumac consumption were evaluated together, it was observed that time significantly influenced insulin levels ($p<0.0001$), while sumac consumption did not have a significant effect($p=0.60$), and there was no interaction between time and sumac ($p=0.99$).

CCK: Fasting plasma CCK levels were similar between the experiments with and without sumac. The mixed meal significantly increased plasma CCK levels at 30 and 60 minutes in the experiments without sumac ($p<0.01$) and at 60 and 90 minutes in the experiments with sumac ($p<0.05$) compared to baseline. The plasma CCK level in the experiments with sumac showed a slightly delayed and prolonged elevation compared to the control experiments, but there was no.significant. difference between the two experiment days at the time points of blood collection. The area under the curve was similar in both experiments. Two-way analyses showed that only time had a significant effect on plasma CCK levels ($p=0.02$), sumac did not have a significant effect ($p=0.67$), and there was no significant interaction between the two factors ($p=0.43$).

GIP: The mixed meal, whether consumed with or without sumac, significantly increased plasma GIP levels at 30, 60, 90, and 120 minutes compared to baseline ($p<0.01$ at 30, 60, and 90 minutes, and $p<0.05$ at 120 minutes for both experiments). There was no significant difference. between the experiment days in terms of the total GIP response or the time points of blood collection. Time had a significant effect on plasma GIP levels ($p<0.001$), while sumac consumption did not have a significant effect, either alone ($p=0.43$) or in combination with time ($p=0.96$).

GLP-1: Plasma GLP-1 levels did not increase above baseline levels in both the experiments with and without sumac. There was no significant difference between the experiment days in terms of the total integrative GLP-1 response or the GLP-1 levels at the time points of blood collection. Two-way analyses showed that time ($p=0.15$), sumac ($p=0.59$), and the interaction between time and sumac ($p=0.88$) did not significantly affect plasma GLP-1 levels.

The effect of sumac on appetite and total energy intake

There was.no.significant difference in terms of hunger levels before breakfast or before lunch between the control experiments and the experiments with sumac.

Similarly, there was.no difference in hunger levels before and after the buffet meal between the experiments. There was no significant difference in total energy intake or the distribution of energy intake according to food groups during the buffet meal.

The effect of sumac on defecation

The stool consistency, as assessed by the Bristol Stool Scale, had a median score of 3 during the control week. However, during the week when 2 grams of sumac were consumed daily, the stool consistency had a median score of 4, and the difference between the weeks was statistically significant ($p < 0.05$). The average number of daily bowel movements was 0.59 during the week without sumac consumption, while it was 0.53 during the week with sumac consumption. However, this difference was not statistically significant ($p = 0.17$).

There was.no.significant difference in the subjective feeling of fullness evaluated before and after dinner between the control week and the week with sumac consumption.

DISCUSSION

This study investigated the potential effects of chili peppers and sumac on various physiological processes, including blood sugar levels, intestinal peptides, appetite, and bowel habits. However, the results did not show significant changes in these parameters compared to the control experiments. These findings suggest that the dosage or duration of use may play a role in eliciting the desired effects. Further research is needed to explore the optimal dosage, duration, and specific components of these spices to fully understand their potential health benefits.

Spices have been used for centuries in various geographical regions, both to enhance the flavor of dishes and to treat various illnesses. Recent studies conducted in various disciplines have begun to shed light on the biological/physiological basis of the healing or digestive effects of spices, demonstrating that they may possess certain properties that could potentially be used as medicine (26,27).

Some of the mechanisms that regulate the secretion of intestinal peptides involved in appetite and gastrointestinal function depend on the perception of luminal nutrients (28,29). Structures involved in this perception include enteroendocrine cells, interneurons, extrinsic nerves, the central nervous system, and taste receptors located in enterocytes. Numerous studies have shown the role of sensory afferent nerves in the secretion of GLP-1, GIP, and CCK, which have been shown to have an impact on appetite and metabolism (30,31). However, it should be noted that there are likely other known and unknown mechanisms involved in the secretion of these peptides.

Animal studies have suggested that the presence of GIP is a prerequisite for the development of adipose tissue and obesity (32,33). To date, no human study has been conducted to investigate whether chili peppers affect GIP secretion. In our study, we investigated the effect of a single meal with added chili peppers on peptides that are secreted from the intestines and have an impact on appetite and metabolism, over a period of 2 hours following the meal, in healthy volunteers. We used a mixed meal that was richer in fat compared to a regular meal in order to stimulate GIP secretion further. According to our results, the administration of 1 g of chili pepper with a relatively fat-rich mixed meal did not cause a significant change in glucose, insulin, CCK, and GLP-1 levels. It flattened the GIP curve, but there was no significant difference in the integrated GIP response between with and without chili pepper. The perceived satiety level determined by a visual scale and the energy content of the meal consumed freely in the buffet did not differ between the experimental days, two hours after this meal. Our findings are not consistent with the results of previous studies. The reason for this discrepancy may be that the amount of capsaicin in the chili pepper used was insufficient to produce an effect. Although we provided a standardized amount of chili pepper by weighing it, we were unable to determine the capsaicin content in the chili pepper used, so we could not compare our study results with other studies. Our findings do not provide insights into the effects of long-term continuous use. The observed flattening in the GIP curve suggests that investigating the effects of larger amounts and longer durations of use would be necessary.

We also investigated whether mechanical stimuli originating from the mouth have any effects on the secretion of intestinal peptides. Various studies have suggested that visual perception of food, odor perception of food, and sham feeding can alter the secretion of intestinal peptides through central mechanisms (34-36). Although the presence of GIP in saliva and its increase with sham feeding have been previously demonstrated, the effect of mechanical stimulation without food contact on plasma GIP secretion is unknown. In our study, we did not observe any changes in plasma peptide levels due to mechanical stimulation without food contact. We did not investigate GIP levels in saliva or total protein content in saliva. Our study is the first to investigate the effect of mechanical stimulation on plasma peptides, and there is no comparable data for comparison.

For the secretion of intestinal peptides that affect appetite and metabolism, nutrients in the lumen need to be present in their broken-down form, absorbed, or bound to a receptor. The secretion of GLP-1 requires glucose binding to the glucose transporter in enterocytes in addition to central reflex mechanisms. The breakdown of carbohydrates and their binding to the transporter is

sufficient for secretion; they do not need to be absorbed. The secretion of GIP is primarily stimulated by fats, and both the breakdown and absorption of fats are required for its stimulation (29,36). CCK secretion is associated with both carbohydrates and fats (38). In order for its secretion to occur, in addition to central reflex mechanisms, the absorption of fatty acids containing more than 10 carbon atoms is necessary.

Sumac is a commonly used spice, and it is a plant with approximately 250 species (39). Various species of sumac have been extracted, and their contents have been determined in Turkey (40). There are numerous experimental studies showing the anti-fibrinogen antiapoptotic, anti-inflammatory, antioxidant, leukopenic, cytotoxic, and hypoglycemic effects of extracts obtained from Sumac (38,40). It is known that sumac extracts exhibit antioxidant effects in diabetics (41-43). The mechanism of action on blood sugar is known to involve the inhibition of alpha-glucosidase and amylase, thereby preventing the breakdown and absorption of carbohydrates (21,44). Since other alpha-glucosidase inhibitors have been used in the treatment. of diabetes, and it has been shown that they increase the secretion of intestinal peptides with incretin-like properties, which are stimulated by carbohydrates in the lumen, it is possible for sumac to have a similar effect.

Based on this possibility, we investigated the effects of consuming 2 grams of sumac with a carbohydrate-rich mixed meal in terms of blood sugar, intestinal peptides, appetite, and total energy consumption in the next meal. There was no difference in glucose, insulin, GIP, GLP-1, CCK responses, appetite, and energy consumption between the sumac and control experiments. The CCK response appeared slightly later and was slightly lower in the Sumac experiment, but the difference was not statistically significant. In this experiment as well, the analysis of the components of the sumac we used was not performed, and the species of the sumac plant was not determined.

To date, no study has been conducted investigating the effects of single-dose sumac consumption on blood sugar. Previous studies have demonstrated hypoglycemic effects using sumac extracts in humans or in vitro environments. However, hypoglycemic effects only occur with long-term use in diabetic patients. The lack of hypoglycemic effect of sumac in this study may be due to the dosage used, single-dose administration, or a small number of subjects. Another possibility is that some species of sumac may have stronger enzyme inhibition properties. It may be more appropriate to evaluate the sumac species used in Turkey and test those that are effective in vitro in humans. The effects of sumac on appetite and the amount of food consumed in the next meal have not been investigated so far. The lack of changes in this study does not provide insights into the effects of continuous and higher doses of sumac use. Sumac is also known to have potential effects on altering carbohydrate digestion in the lumen and exhibiting antibacterial properties (45-47). Therefore, we investigated its effects on bowel habits. Continuous use of 2 grams of sumac for one week did not change the frequency of bowel movements but softened the stool consistency. The observed effect in our experimental setup does not provide information on whether it is related to intestinal flora, carbohydrate digestion, direct mucosal irritation, or any other effect of sumac. This study did not investigate intestinal flora, stool osmolarity, carbohydrate digestion, and antioxidant capacity.

Limitations of the Study

1.Dosage and duration: The study used a single dose of chili pepper and sumac, and the effects were measured over a relatively short period of time (2 hours). The study does not provide insights into the effects of long-term or higher doses of spice consumption.

2.Lack of human GIP study: While animal studies have suggested the role of GIP in adipose tissue development, no human study has been conducted to investigate the effect of chili peppers on GIP secretion. This limits the understanding of the potential impact of chili peppers on GIP levels.

3.Mechanical stimulation: The study investigated the effect of mechanical stimulation on plasma peptide levels without food contact. However, it did not measure GIP levels in saliva or total protein content in saliva, making it challenging to compare the findings with other studies.
4.Lack of analysis and identification: The study did not analyze the specific components or species of the sumac used, limiting the understanding of its potential effects. Different species of sumac may have varying properties, and further investigation is needed to determine their efficacy.
5.Limited sample size: This may limit the statistical power and generalizability of the results.

6.Lack of comprehensive analysis: The study did not investigate several factors related to the effects of spices, such as intestinal flora, stool osmolarity, carbohydrate digestion, and antioxidant capacity. These additional analyses could provide a more comprehensive understanding of the mechanisms and effects of spices on physiological processes.

7.Lack of comparison data: The study mentions the absence of comparable data for certain measurements, making it difficult to contextualize and compare the findings with previous studies.

Conclusion

The spices used in the doses we administered did not alter the secretion of intestinal peptides with single-

dose use, but one week of sumac consumption softened stool consistency. Our findings suggest that evaluating the effects of long-term and high-dose use may lead to the discovery of a potential treatment for diabetes and/or constipation.

DECLARATIONS

Ethical approval: This is a Specialization Thesis and was approved by the Marmara University ethical committee (Decision No: MAR-Y4-2009-0226, Date: 5 June 2009).

This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subject

Conflict of interest: The authors declare no conflicts of interest.

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Original Article

Diabetes Mellitus is Frequent, But Retinopathy is Rare in Acromegaly: A Cross-sectional Study

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ABSTRACT

Background: The roles of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in diabetic retinopathy (DR) are well recognized, but the prevalence and pathogenesis of retinopathy in acromegaly are not fully understood. We established the frequency and severity of glucose intolerance and retinopathy—and the relationship between them—in patients with acromegaly.

Methods: All patients with acromegaly under the care of the Department of Endocrinology, Başkent University Hospital were enrolled. Fundoscopy was carried out by two experienced ophthalmologists. Acromegaly disease state was evaluated by basal GH and IGF-1 measurements, and an oral glucose tolerance test (OGTT) when appropriate. Glucose tolerance states were assessed by means of fasting and postprandial plasma glucose concentrations, glycohemoglobin measurement and an OGTT when appropriate. The relationships between retinopathy, acromegaly disease activity and glucose tolerance states were examined.

Results: The cohort comprised 49 patients with acromegaly (24 women), with a median disease duration of 25 months (range 1–420 months). Thirty-three had active disease, with median concentrations of GH of 5.54 ng/ml (0.72–172 ng/ml) and IGF-1 of 541.5 ng/ml (203–1.985 ng/ml). The prevalence of diabetes mellitus (DM) was 30.6% (n = 15; 10 patients had active acromegaly, five of whom had uncontrolled DM). Two patients had retinopathy (4.1%); both had active acromegaly and uncontrolled DM at the time of examination.

Conclusions: The prevalence of DM was twice that of a reference population, but that of DR was lower than expected. Our findings suggest that disease activity in acromegaly might not contribute to retinopathy.

Keywords: Acromegaly, retinopathy, growth hormone, diabetes mellitus, insulin-like growth factor 1

INTRODUCTION

Diabetic retinopathy (DR) is a chronic microvascular complication of diabetes mellitus (DM) that can lead to loss of vision. Many factors have been identified that contribute to the pathogenesis of retinopathy, either independently or together with hyperglycemia and its underlying factors (1-3).

The potential roles of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in DR have been evaluated in vitro and in vivo (3,4-6), and it has been reported that locally produced GH or IGF-1, and in some cases systemic GH and IGF-1 activity, may contribute to the onset of retinopathy or exacerbate it (5,7-10). Acromegaly is caused by the chronic hypersecretion of GH, and is often accompanied by glucose intolerance, DM or retinopathy (11). Although these complications are well recognized, understanding of their prevalence, severity and pathogenesis is incomplete, and is informed by case reports and a small number of case series, mostly of 10 to 15 cases (12-18).

Surveillance for retinopathy is not routine in acromegaly, but it would be important to establish screening programs if there are other currently unrecognized factors other than chronic hyperglycemia that might predispose patients with acromegaly to retinopathy. We aimed to assess the frequency and severity of impaired glucose tolerance and retinopathy, and the extent of any relationship between the two, in a relatively large cohort of patients with acromegaly with a variety of disease activity states treated in a tertiary referral center.

METHODS

Study participants

We consecutively recruited all patients with acromegaly who attended for regular follow-up at the Endocrinology Departments of the two main clinical centers of Baskent University Faculty of Medicine between November 2009 and December 2010 to our cross-sectional study. The Baskent University Ethics Committee for Human Studies approved the protocol, and all participants provided informed consent.

Acromegaly was diagnosed as follows. Initially, baseline blood GH and IGF-1 concentrations were measured. A 75 g oral glucose tolerance test (OGTT) was undertaken in those who had an IGF-1 concentration in excess of their age- and sex-matched upper limit of normal. Those individuals with nadir GH concentration >1 ng/ml during an OGTT were diagnosed with acromegaly. The disease was regarded as biochemically controlled when nadir GH concentration was <1 ng/ml during an OGTT, and IGF-1 concentration was within the age- and sex-matched normal range (19).

Diabetes mellitus was diagnosed in those with a fasting plasma glucose (FPG) concentration ≥126 mg/dl on at least two occasions, or those with a plasma glucose concentration ≥200 mg/dl in the second hour of an OGTT, or a random plasma glucose concentration ≥200 mg/dl for those with symptoms of hyperglycemia. Individuals with FPG concentration between 100 mg/dl and 125 mg/dl, and/or a postprandial second hour glucose concentration between 140 mg/dl and 199 mg/dl were defined as pre-diabetic. The definition of glycemic control was a glycohemoglobin (HbA1c) concentration <7% (20).

Assessment of Acromegaly

Acromegaly disease state was evaluated by basal GH and IGF-1 measurements, and GH measurement during an OGTT where appropriate. Glucose tolerance states were assessed by FPG and postprandial plasma glucose concentration, HbA1c measurements and OGTT where appropriate. Glucose tolerance state, GH and IGF-1 data, and other relevant history at the time of acromegaly diagnosis were obtained from the hospital records.

Standard fundoscopy was undertaken by two experienced ophthalmologists (DA and SS; one for each center), who were unaware of the clinical status of each patient. The pupil was dilated with one drop of 0.5% tropicamide and 2.5% phenylephrine 30 minutes beforehand. Pathologic findings in the retina were classified according to the criteria in Table 1 (21). Fundus fluorescein angiography (FFA) was performed if there was evidence of retinopathy. The relationships between retinal findings, acromegaly disease activity and glucose tolerance states were examined.

Laboratory analyses

Venous blood samples were taken after at least 8 hours of fasting between 08.00-09.00 am. Plasma glucose concentration was measured by the hexokinase method (Roche/Hitachi P modular autoanalyzer, Roche Diagnostics, Mannheim, Germany); the normal range was 70–99 mg/dl. The proportion of HbA1c was measured by means of the turbidimetric inhibition immunoassay (Roche Diagnostics); the normal range was 4% to 6%. Growth hormone concentration was measured using solid phase two-site chemiluminescence immunometric

Table 1. Classification of diabetic retinopathy (21)

Classification Level	Defining features
Retinopathy absent	No apparent lesion
Mild NPDR	Microaneurysm, hemorrhage, soft exudate, increase in vascular permeability
Moderate NPDR	Microaneurysm and hemorrhage with increased severity, vascular closure
Severe NPDR	More than 20 intraretinal hemorrhages in four quadrants or venous beading in two or more quadrants, or intraretinal microvascular abnormalities in one or more quadrant but not PDR
PDR	Presence of one or more of the following: • Neovascularization of the optic disc • Neovascularization elsewhere • Preretinal hemorrhage • Vitreous hemorrhage • Fibrous tissue proliferation

NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 2. Demographic and clinical characteristics of patients with acromegaly at diagnosis

Number of cases (F/M)	Age (years, mean ± SD)	Maximum size of adenoma (mm, mean ± SD) *	GH (ng/ml, median) (range)	IGF-1 (ng/ml, median) (range)	Glucose tolerance state, n (proportion)
49 (24 / 25)	41.4±11.4	All (49): 18.9±9.7 Micro (8): 7.5±2.5 Macro (41): 21.1±9.0	16.8 2.0–128.0	745 261–2.923	Normal: 19 (38.8%) Pre-diabetes: 18 (36.7%) Diabetes mellitus: 12 (24.5%)

F, female; M, male; SD, standard deviation; n, number of cases; Micro, microadenoma; Macro, macroadenoma; GH, growth hormone; IGF-1, insulin-like growth factor-1.* p <0.001

assays (Immulite 2000, Siemens Healthcare Diagnostics, Deerfield, IL, USA); the reference range was [0-1 ng/ml], and IGF-1 concentration using a solid-phase enzyme-labeled chemiluminescence immunometric assay (Immulite 2000, Siemens Healthcare Diagnostics); the reference range was [94-252 ng/ml].

STATISTICAL ANALYSIS

Data analysis was undertaken using SPSS software (Statistical Package for the Social Sciences, version 15.0, SSPS Inc., Chicago, IL, USA). Demographic data were subject to frequency analyses and reported as the median (range), or mean ± standard deviation (SD). The chi-squared, Student t and Mann-Whitney tests were used to evaluate numerical data. For all evaluations, a significance level of p <0.05 at a 95% confidence interval was accepted as statistically significant.

RESULTS

In total, 49 patients with acromegaly were enrolled; their characteristics at the time of diagnosis are shown in Table 2. Thirty had glucose metabolism disturbance (61.2%), and twelve had DM (24.5%). Twenty-three patients underwent surgery (46.9%) and the remaining twenty-six (53.1%) were managed medically as the primary treatment modality. Thirteen of those who had surgery underwent transsphenoidal adenomectomy (56.5%), while a transcranial approach was used in the remaining ten (43.5%). Half of the 26 treated medically were treated with octreotide and the other half were treated with monthly injections of lanreotide.

The biochemical and retinal findings, and glucose tolerance states of active and controlled cases of acromegaly at the time of evaluation, are shown in Table 3. Biochemical control had been achieved in 16 of the patients (32.7%) at the time of evaluation, a median of 25 months after diagnosis (range 1–420 months). The prevalence of DM and impaired glucose tolerance were similar in those with active or controlled disease (Table 3). Eleven patients had arterial hypertension controlled with antihypertensive drugs.

Fifteen patients in the study had DM (30.6%); their demographic and clinical characteristics are shown in Table 4. Seven of the 49 patients (14.3%) had already been diagnosed with DM before acromegaly. Diagnosis of DM and acromegaly were made simultaneously in five patients. The remaining three patients developed DM during the study period. All patients recognized to have DM had undergone fundoscopy in the previous 6 months. Of the five patients with poorly controlled DM, two had DR. Both exhibited bilateral punctuate hemorrhage and hard exudates. In one patient with an HbA1c of 9.2%, FFA revealed diffuse microaneurysms and neovascularization consistent with proliferative DR. In the other, who had an HbA1c of 8.6%, there was no evidence of neovascularization, and the findings were

Table 3. Clinical, laboratory features and retinal findings of the study group during evaluation

Acromegaly cases (n=49)	**Age yerars, mean ± (SD)****	**Time since diagnosis (months, median)**(range)**	**Basal GH (ng/ml), median)***(range)**	**IGF-1 (ng/ml), median)****(range)**	**Glucose tolerance state, n (proportion)**	**Retinopathy, n (proportion)**
Active disease* (n=33)	46.1±11.7	12.5 (1–104)	5.54 (0.72–172.0)	541.5 (203.0–1,985.0)	Normal: 12 (37%) Pre-diabetes: 11 (33%) Controlled DM: 5 (15%) Uncontrolled DM: 5 (15%)	2 (6.1%)
Controlled disease* (n=16)	44.5 ±12.9	40 (7–420)	1 (0.17–2.5)	162.0 (68.9–348.0)	Normal: 4 (25%) Pre-diabetes: 7 (44%) Controlled DM: 5 (31%) Uncontrolled DM: 0 (0%)	0 (0%)

N, number; SD, standard deviation; min, minimum; max, maximum; GH, growth hormone; IGF-1, insulin-like growth factor-1; DM, diabetes mellitus. * Biochemical control; ** p>0.05; *** p<0.01; **** p<0.001

Table 4. Clinical features of individuals diagnosed with diabetes mellitus during the study period

Case no.	At the time of acromegaly diagnosis				At the time of evaluation			
	DM duration (years)	FPG (mg/dl)/ HbA1c (%)	DM therapy	Basal GH/ IGF-1 (ng/ml)	FPG (mg/dl)/ HbA1c (%)	DM therapy	Basal GH/ IGF-1 (ng/ml)	Acro duration (years)/disease state
1[#]	10	268/9.0	MNT, OAD	38.5 / 597	186/8.6	MNT, insulin	15.3 / 447	0.5 / A
2	0	112/5.8	recent dx	98.0 / 905	121/6.1	MNT, OAD	4.3 / 880	2 / A
3	0	161/6.8	recent dx	3.2 / 550	93/5.5	MNT, OAD	0.2 / 223	5 / C
4	6	148/8.4	MNT, OAD	41.5 / 1.850	116/7.4	MNT, OAD	0.8 / 397	1 / A
5	0	88 / 6.6	recent dx	17.2 / 504	91/5.6	MNT	0.5 / 158	4 / C
6	0	87/6.5	recent dx	19.4 / 859	87/6.1	MNT	1.0 / 221	2.5 / C
7	3	134/6.9	MNT, OAD	27.5 / 938	115/6.5	MNT, OAD	17.6 / 593	4.5 / A
8[¥]	-	123/ -	-	4.5 / 745	126/6.7	MNT	1.5 / 475	1 / C
9[¥]	-	109/-	-	23.0 / 735	131/6.6	MNT	1.4 / 212	3 / C
10[¥]	-	121/-	-	11.7 / 2.923	136/6.6	MNT	12.0 / 1970	0.5 / A
11	10	154/6.4	MNT, OAD, insulin	40.0 / 1.985	154/6.4	MNT, OAD, insulin	40.0 / 1.985	0 / A
12	0	137/5.5	recent dx	7.3 / 477	121/6.3	MNT, OAD	5.7 / 715	1 / A
13	10	186/10	insulin	16.3 / 517	186/10.0	insulin	16.3 / 517	0 / A
14	5	176/8	MNT, OAD	11.2/ 980	115/7.9	MNT, OAD	5.7 / 812	7 / A
15 [#]	12	312/10	MNT, insulin	21.4/ 550	174/9.2	MNT, insulin	5.37 / 553	3 / A

DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, glycohemoglobin; GH, growth hormone; IGF-1, insulin-like growth factor-1; Acro, acromegaly; MNT, medical nutrition therapy; OAD, oral antidiabetic drug; A, active disease; dx, diagnosis; C, controlled disease. [#]cases with retinopathy, [¥] pre-diabetic at diagnosis of acromegaly

suggestive of mild to moderate non-proliferative DR (Table 4) (21). Progression or deterioration of the retinal changes was not detected in both cases during the study period.

Other than these two established cases of retinopathy, fundoscopy undertaken as part of this study did not identify any other affected patients, including the three other patients with active acromegaly and poorly controlled DM (Tables 3 and 4). The biochemically controlled acromegaly group included five patients with controlled DM (Tables 3 and 4).

There was no significant difference in the proportion of patients with controlled or active acromegaly in the subgroup with normal glucose tolerance (n=4 (25%) vs n=12 (75%)) and the group with abnormal glucose tolerance (pre-diabetes [n=7 (38.9%) vs n=11 (61.1%)] and DM [n=5 (33.3%) vs n=10 (66.7%)], respectively, $p<0.05$ for all).

Approximately 80% (n = 39) of patients were being treated with somatostatin receptor ligands (SRL) at the time of evaluation. Eight patients had received radiotherapy; acromegaly was controlled only in two of these cases, but neither had DM.

DISCUSSION

Glucose intolerance is one of the most important sequelae of acromegaly; when DM is diagnosed in a patient with acromegaly, it adds substantial additional therapeutic and pathophysiologic burdens (11). In our group of 49 patients with acromegaly, the prevalence of DM was 30.6% and DR was 4.1%. A national survey conducted in 2010 (TURDEP 2) reported that the prevalence of DM in the adult population of Turkey was 13.7% (22). The high prevalence of DM in our cohort of patients with acromegaly was not a surprising finding, given that acromegaly is a well-recognized cause of impaired glucose homeostatis (20). Moreover, in a study of 2,270 patients with DM and pre-diabetes, the prevalence of acromegaly was 0.13%, and that was higher than the general population (23,24). The prevalence was not sufficiently high to warrant a recommendation for screening for acromegaly in patients with DM, but strategies have been recommended to detect this chronic, slowly progressing disease more promptly (23).

The prevalence of DM in patients with acromegaly was

reported between 17-60% (15,25-30) in previous studies. These cohort studies included 34-200 participants (15,25-29). Our findings were broadly comparable with the study of Fieffe et al, which is the most comprehensive study in the field (30). The prevalence of DM was 22.3% among 519 patients in the French Acromegaly Registry and that while age, body mass index (BMI) and arterial hypertension were risk factors, blood GH and IGF-1 concentrations were not (30).

In a more recent study, besides age and BMI, a family history of DM and elevated IGF-1 (but not GH) concentration were found to be associated with impaired glucose metabolism in patients with acromegaly (29). Schneider and colleagues investigated whether IGF-1 concentration predicts the development of DM in two large prospective cohort studies. The blood IGF-1 concentration of 7,777 non-diabetic individuals was measured and they were followed prospectively. Abnormally high and low IGF-1 concentrations were associated with new onset DM in 464 cases during a 5-year follow-up period (31).

Diabetic retinopathy generally appears about 5 to 10 years after the onset of hyperglycemia. Receptors for GH and IGF-1 are strongly expressed in the retina; stimulation of these receptors by their ligands results in proliferation of the retinal epithelium (32). However, reports on the role of the GH/IGF-1 system, locally or systemically, in the pathogenesis of DR are inconsistent. As the IGF-1 receptors are expressed by groups of cells with diverse functions, and the findings of studies of activation or inhibition of the systemic GH/IGF-1 system on retinal neovascularization are inconsistent, the roles of the GH/IGF-1 axis in the pathogenesis of retinopathy are complex and probably indirect. Therefore, the activity of the GH/IGF-1 system in the retina and its role in the pathogenesis of DR has been debated (3,4-10, 33-39). Given the over-activity of the GH/IGF-1 system in acromegaly, the reported rates of retinopathy in acromegaly are surprisingly low, and severe retinopathy is rare (13,14).Retinopathy caused by DM developing secondary to acromegaly is a very unusual complication (40). Understanding of retinopathy in acromegaly is somewhat limited; most evidence is based on case reports (12-18). Despite the findings of elevated intraocular GH and IGF-1 concentrations in many of these studies and case reports, a direct relationship between acromegaly and retinopathy has not yet been established (3,4,41). While retinopathy may be a consequence of dysfunction of the GH/IGF-1 system, it is more likely that it is a complication of impaired glucose homeostasis in patients with uncontrolled DM (12,17,41).

Cases of unexpectedly severe DR in the context of mild glucose intolerance have been reported in patients with acromegaly, in which the retinopathy has been attributed to elevated GH concentration (42). Tran and colleagues reported a patient with recently diagnosed diet-controlled type 2 DM, active acromegaly and severe DR, in whom the retinopathy and DM recovered almost completely about 18 months after surgery for acromegaly (16). The authors proposed that the severity of DR in this case could not be explained by DM alone, and that high GH concentration was probably the cause of the retinal angiogenesis. Similarly, the prevalence of proliferative retinopathy was determined to be 9.3% among both 43 cases with acromegaly and 129 cases with type 2 DM in a recent study. No non-proliferative retinopathy was observed among acromegaly cases. The authors suggested that IGF-1 may play an important role in proliferative retinopathy (43). In one recent prospective observational study, 8.8% of 91 acromegalic and 9.8% of 123 cases with impaired fasting glucose developed retinopathy at the end of a median follow-up of 64 months. Patients with acromegaly had the same incidence of non-proliferative retinopathy and a non-statistically significantly higher incidence of proliferative retinopathy (OR 2.461; 95% CI 0.404–14.988). The authors concluded that GH and IGF-1 might play a crucial role in the development of proliferative retinopathy and acromegalics should be screened similar to diabetes patients (44).

The median disease duration of our cohort was more than 2 years after diagnosis (one patient had a greater than 30-year history of acromegaly). Some patients had markedly elevated blood GH concentration (>100 ng/dl) or an IGF-1 concentration of approximately 2,000 ng/ml, but nonetheless, there were only two cases of retinopathy. DM was longstanding (>9 years), poorly controlled (HbA1c >8%), and retinopathy had been detected before the diagnosis of acromegaly in both cases. Our finding that there were no additional cases of retinopathy, even among 33 patients with active acromegaly, suggests that disease activity may not contribute to DR in acromegaly. A nationwide multicenter study undertaken in Turkey in 2000 found that the prevalence of DR was 30.5% in 2,362 patients with DM (45). Our finding of only two cases of DR (13.3% of the 15 patients with DM) is therefore lower than expected, but could be explained by the relatively short history of DM in our cohort: about two-thirds of patients had not been diagnosed with DM before acromegaly.

The results of a similar study by Ballintine and colleagues are broadly comparable with ours: they detected one case of retinopathy in 44 patients with acromegaly (2.2%), compared with two cases (4.1%) in our cohort of 49 (13). More than half of their patients had pre-diabetes with a mean duration of 2 years, supporting the hypothesis that DR is a consequence of uncontrolled DM rather than dysfunction of the GH/IGF-1 system. In other, differently designed studies, the prevalence

of retinopathy in acromegaly has been reported to vary between 0% and 20% (14,15,18). In one of these studies, 10 of the 15 patients with acromegaly had DM, and three of the 10 were reported to have DR (14). There was also reportedly just one case of DR (2.9%) in a patient who also had DM, in another cohort of 34 patients with acromegaly (15). In one study, DR was detected in 12.5% of 40 patients with acromegaly, all of whom also had DM. The duration and severity of DM was not clear in all patients. There was a significant relationship between DR and hyperglycemia, but no correlation was determined between DR and GH concentration (18). The variety of study designs and cohort sizes (most of which comprise 10–15 patients with acromegaly) probably account for these diverse findings (12-18).

A relatively high proportion of patients in our study group received primary medical therapy (49%). This was partially due to the presence of comorbidities that increased perioperative anesthetic and surgical risk for some patients, and personal preference in others. This likely explains the lower rates of disease control in our group (39%) compared with other tertiary referral centers (11).

As there were only two cases of DR in our group, we could not reliably establish the influence of age, disease duration, or GH and IGF-1 concentrations, on the risk of developing retinopathy. However, in the light of the body of evidence in the literature and our findings, it is our opinion that the onset and progression of DM and DR are likely independent of the GH/IGF-1 dysfunction seen in acromegaly.

Preclinical data on the therapeutic role of somatostatin in DR is encouraging, and there are an increasing number of clinical trials, especially of octreotide (46,47). Somatostatin receptor ligands have two mechanisms of action, exerting direct anti-angiogenic, anti-proliferative and anti-apoptotic effects, and acting indirectly by suppressing the GH/IGF-1 axis (47). Considering that almost 80% of our group were being treated with an SRL, we cannot exclude the possibility that this therapy effectively prevented retinopathy in the majority of the active acromegaly group other than the two patients in whom DR had already been documented. The active acromegaly group comprised all five of the cases of uncontrolled DM, including the two patients with retinopathy, which makes it difficult to draw any firm conclusions about the effect of SRLs on retinopathy in acromegaly. Recently, multimodal management of a patient with proliferative diabetic retinopathy and diabetic macular edema associated with active acromegaly, who presented with deteriorated eyesight, was reported. Anti-vascular endothelial growth factor treatments, cataract surgeries and retinal direct laser photocoagulation were performed together with gradual glycemic control with basal insulin to prevent worsening of the visual impairment. She was given an injection of a long-acting somatostatin analog (octreotide LAR), followed by a trans-sphenoidal adenomectomy. Her visual acuity improved without worsening of retinopathy (48).

Our study has several limitations: the sample size was relatively small, and the lack of a control group made it difficult to account for all the potentially confounding factors. Nonetheless, our findings enlighten about the relationship between retinopathy, DM and acromegaly in an era where the prevalence of DM has doubled in almost 10 years (22). It is also encouraging that we found no new cases of retinopathy, even in those with active acromegaly and uncontrolled DM. Most of our patients with acromegaly are treated with an SRL. While these drugs can influence glucose metabolism, it is thought that the clinical consequences are minimal (11,49).

It will be important to undertake prospective controlled studies of large cohorts of patients to fully understand the role of the GH/IGF-1 system in the onset and progression of retinopathy in acromegaly, allowing subgroup analysis to be undertaken to establish the influence of DM or other potentially confounding factors.

CONCLUSION

The prevalence of DM in patients with acromegaly was more than twice that of a reference population, but that of diabetic retinopathy was surprisingly low in a group in which biochemically active cases of acromegaly predominated. Those cases with retinopathy had uncontrolled DM, which suggests that disease activity in acromegaly might not contribute to retinopathy. Prospective long-term studies of larger cohorts will be needed to validate our findings.

DECLARATIONS

Conflict of interest: The authors declare that they have no conflict of interest.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors' contributions: All authors contributed in some way to the concept and design of the study; acquisition, analysis and interpretation of data; and writing or revising the manuscript.

Ethics Committee: Başkent University, IRB; 2009/KA09/334

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Original Article

Evaluation of Cardiovascular Autonomic Neuropathy in Patients with Hypertensive Type 2 Diabetes Mellitus

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ABSTRACT

Background: A non-invasive test called heart rate variability (HRV) and heart rate turbulence (HRT) uses sinus node rates and the sinus node rates' deceleration after premature contractions of the heart to identify cardiovascular autonomic dysfunction. The incidence of type 2 diabetes mellitus (DM), which continues to be the most significant health issue, is rising. Combining DM and hypertension raises the risk of heart disease. Our goal was to assess the impact of HRV and HRT analyses on cardiac autonomic functioning in diabetic patients who have hypertension.

Methods: A total of 108 DM patients, 50 normotensives, and 58 hypertensives were involved in this cross-sectional study. Outpatients had 24-hour Holter monitoring, and all recordings were evaluated and cleared of artifacts afterwards. After that, HRT and HRV analyses were performed.

Results: Age, gender, and comorbidity were similar across the study groups. The HRV parameters of SDNN (103.7±2.5, 113.6±1.68, p=0.002), and SDANN (95.1±2.3, 103.2±2.1, p=0.014) were significantly lower in the hypertensive DM group. The HRT values did not significantly differ between the two groups.

Conclusions: In our study, asymptomatic hypertensive DM patients showed a significant decline in HRV parameters. Patients who have both diabetes and hypertension are more likely to exhibit autonomic dysfunction, as seen by HRV. As a result, these people need to be monitored more carefully for cardiovascular diseases.

Keywords: Diabetes Mellitus, hypertension, autonomic dysfunction, heart rate variability, heart rate turbulence

INTRODUCTION

Considering the high rates of mortality and morbidity, type 2 diabetes mellitus (T2DM) is still a major global health concern. Its incidence has been increasing dramatically over time. Particularly, DM nearly doubles the risk of cardiovascular mortality. It has a direct correlation with a higher risk of peripheral artery disease, myocardial infarction, heart failure, stroke, and coronary heart disease (1). Having DM and hypertension (HT) increases the risk of cardiovascular heart disease (CVD) (2).

Previous research has demonstrated that diabetic hypertensives are at increased cardiovascular risk than normotensive diabetics despite maintaining good glycemic and blood pressure control (3). Both conditions provide serious cardiovascular problems, which are one of the main causes of death throughout. Therefore, HT and DM prevention and aggravation pose major concerns (4).

One of the most significant DM consequences, cardiovascular autonomic dysfunction (AD), is frequently overlooked by healthcare professionals (5). Patients with DM can have several clinical manifestations of AD. It is common to see diurnal heart rate variability, resting tachycardia, and diminished reflex responsiveness. Additionally, there are left ventricular dysfunction, ischemia, painless myocardial infarction, and sympathovagal blood pressure imbalance. Another theory is that sudden mortality in diabetes individuals is brought on by QT-interval prolongation, which is linked to the imbalance between parasympathetic and

sympathetic innervation (6). Several methods, including heart rate variability (HRV) and heart rate turbulence (HRT), can be used to evaluate AD (7). Previous studies have demonstrated reduced HRV and deterioration of HRT to predict increased cardiac mortality (8,9). HRV and HRT are frequently used to diagnose AD and potentially identify patients who pose a risk. It is noteworthy that hypertensive DM patients experience a higher frequency of cardiovascular events, and these patients need to undergo an extensive evaluation of AD. Evaluation of the relationship of the two major risk factors for CV mortality, hypertension and diabetes, is an important issue. In this work, we sought to determine the impact of HRV and HRT analysis on cardiac autonomic functions in relation to the presence of hypertension in diabetic individuals.

METHODS

This cross-sectional study included 108 outpatients with T2DM in total, 50 of them had normotensive blood pressure and 58 had hypertension. These patients were those who visited the outpatient clinic on a regular basis for routine care but hadn't developed any symptoms at the time. This study was conducted at the Afyonkarahisar State Hospital and the Afyonkarahisar Health Sciences University between July 1, 2019, and March 1, 2020. Using admittance numbers that were specific to each patient, we were able to obtain epidemiological, demographic, clinical, and laboratory data from the medical records of the patients. All participant laboratory findings have been collected from patient files, and blood samples tested after a 12-hour fasting period. All participants completed an informed consent form; the study was carried out in accordance with the Declaration of Helsinki; and it was authorized by the institutional local ethics committee (Number: 2019/213).

All patients completed a 24-hour course of Holter monitoring using Reynolds Medical's Pathfinder Holter Software Version 8.255, after which all Holter recordings were analyzed. A computer program (HRT View, Version 0,60-0,1 Software Program, Munich, Germany) automatically calculated the HRT parameters, turbulence onset (TO), and turbulence slope (TS). Before analysis, each contraction that the software determined to be a premature ventricular contraction was visually assessed, and artifacts were removed from the research. HRT was determined using the turbulence onset (TO) and turbulence slope (TS) parameters. The degree of early sinus rate acceleration that followed premature ventricular contraction was referred to as T0. The time constant (TS), which was measured in milliseconds per contraction, was defined as the rate of deceleration after the early sinus rate acceleration. The highest positive regression slope across any five consecutive sinus rhythm RR intervals, out of the RR interval of the first 15 sinus rhythms following premature ventricular contraction, was used to compute the target slope (TS). According to advice given by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, an HRV analysis was conducted (10). The time-domain method was used in the measurement of HRV. SDNN (estimates total HRV, Standart deviation of NN intervals), SDANN (standart deviation of the averages of normal to normal intervals in all 5-minute segments of the entire recording, estimates 24hr. components of HRV), pNN50 (percentage of successive RR intervals that differ by more than 50 ms, estimates short-term components of HRV), RMSSD (root mean square of successive RR interval differences, estimates short-term components of HRV), Tİ (triangular index, total number of all normal to normal intervals divided by the height of the histogram of all normal to normal intervals measured on a discrete scale with bins of 7.8125 ms) values were obtained.

Definitions

Patients with a history of oral anti-diabetic and/or insulin therapy, fasting blood sugar measurements ≥126 mg/dL at least twice, hemoglobin A1C levels ≥ 6.5%, a 2-hour plasma glucose value above 200 mg/dL following a 75-gram oral glucose tolerance test, and/or a random plasma glucose analysis above 200 mg/dL in a patient with classic hyperglycemia symptoms were all considered to have diabetes mellitus (DM) (11,12). Patients who were previously on antihypertensive therapy or those with blood pressures measured at least twice ≥ 140/90 mmHg, and who had an ABPM measurement average above 140/90 mmHg were considered hypertensive, but newly diagnosed patients (within the last 1 months) were not included in the study (13). Also, patients who had critical coronary stenosis, and patients undergoing percutaneous transluminal coronary angioplasty or stenting, and those who had undergone coronary bypass surgery were defined as having CAD (14). The presence of kidney damage or an estimated glomerular filtration rate less than 60 ml/min/1.73 m^2, persisting for 3 months or more, were considered chronic kidney disease (CKD) (15). The term chronic obstructive pulmonary disease (COPD) refers to spirometry-based evidence of lung airflow limitation. Smokers were defined as patients who had used tobacco products within the previous month.

Exclusion Criteria

Patients with hormonal disorders (such as thyroid dysfunction), Type 1 DM, pregnancy, those under the age of 18 and over the age of 65, atrial fibrillation, heart failure, autonomic nervous system disorders, neurological diseases, major infections and those on antiarrhythmic medications were excluded.

STATISTICAL ANALYSIS

Statistical analyses were conducted using SPSS software version 23.0. determine the normal distribution of variables. Normally distributed variables were expressed as mean and standard deviation and non-parametric variables as median and interquartile. Nonparametric data were compared using Mann–Whitney U test and Parametric data with T-test. Also, a Chi-square test was used to compare ordinal and categorical variables. A P-value <0.05 was considered statistically significant.

RESULTS

The average age of the hypertensive group was 53.5±0.83 and of the normotensive group 54.1±0.76. There was no significant difference between the groups in terms of their gender, smoking status, have a chronic disease or BMI values. Among the groups included in the study, the total cholesterol value was significantly higher and HDL cholesterol was significantly lower in the hypertensive T2DM group (p=0.033, p=0.006, respectively). The drug use, laboratory results, and all variable of patients were shown in **Table 1**.

The HRV parameters of SDNN (103.7±2.5, 113.6±1.68, p=0.002), SDANN (95.1±2.3, 103.2±2.1, p=0.014) were significantly lower in the hypertensive T2DM group. The other HRV and HRT parameters did not differ between the two groups (**Table 2**).

Additionally, a correlation analysis study was carried out to see how HRV and HRT parameters related to other variables, but no significant correlations were identified.

DISCUSSION

Disorders of autonomic balance developing in diabetic patients in the form of a marked decrease in parasympathetic tone and a relative increase in sympathetic tone are among the known features of diabetes. Particularly, hyperglycemia and hyperinsulinemia raise sympathetic tone in the cerebral canters that regulate the autonomic nervous system. In diabetics, the onset of cardiac autonomic neuropathy, which can result in arrhythmia, silent infarction, and sudden death, is a poor prognostic predictor. In our investigation, patients with diabetes and hypertension underwent combined HRV and HRT analyses. The largest likelihood of autonomic dysfunction with lower HRV values was seen in subjects with both DM and HT. This group of patients can be evaluated for more frequent and earlier in terms of cardiovascular diseases. A decline in HRV indicates increased sympathetic tone and decreased parasympathetic tone. It has long been thought to have a detrimental effect on the prognosis of cardiovascular disease (16). The co-existence of DM and systemic arterial HT is very common, and some studies have evaluated this situation using time-and frequency-domain HRV analysis. In a study of Nagy et al., hypertensive patients were parted according to the presence of DM and compared with the control group, all HRV parameters of hypertensive patients were found to be lower than the control group. However, when hypertensive patients were evaluated according to the presence or absence of DM, there were no significant differences (17). A small number of diabetics may be the cause of this result. Patients were separated into 4 groups according to DM and HT in Istnes et al.'s study, and each group's performance was assessed using frequency domain analysis. The study's findings indicated that diabetes has a greater impact on HRV measures than does hypertension. Patients with diabetes and hypertension had the highest likelihood of having poor heart rate variability, according to the same study

Table 1. Baseline demographic and clinical characteristics of normotensive and hypertensive Type 2 DM patients

Variables	HT-2DM+ (n:50)	HT+T2DM+ (n:58)	P value
Women, n (%)	24 (%48)	26 (%51)	0.356*
Smoker, n (%)	13 (%26)	14 (%24.1)	0.824*
CAD, n (%)	16 (%24.1)	11 (%24.1)	0.119
CRD, n (%)	6 (%12)	10 (%17.2)	0.445
COPD, n (%)	7 (%14)	8 (%13,8)	0.975
DM duration, year	5.8±1.6	5.4±1.7	0.265
Age (years)	54.1±0.76	53.5±0.83	0.589
BMI (kg/m²)	27.8±0.19	28.3±0.28	0.734
Fasting glucose (mg/dl)	159.1±2.36	161.4±2.59	0.872
HbA1c (mg/dl)	7.84±0.81	7.89±0.12	0.788
Creatinine (mg/dl)	0.83±0.03	0.86±0.21	0.390
Hemoglobin (g/dl)	13.8±0.17	13.9±0.2	0.832
Neutrophile count (x10³/uL)	5.52±0.22	5.63±0.23	0.729
Lymphocyte count (x10³/uL)	2.09±0.09	2.15±0.09	0.657
Monocyte count (x10³/uL)	0.61±0.03	0.68±0.04	0.893
Platelet count (x10³/uL)	259.7±8.4	262.4±9.8	0.921
Total Cholesterol (mg/dl)	156.3±4.1	172.7±6.2	0.033*
Triglyceride (mg/dl)	265.9±4.5	258.3±10.9	0.545
HDL Cholesterol (mg/dl)	45.1±0.71	42.2±0.66	0.006*
LDL Cholesterol (mg/dl)	139.1±4.5	148.8±4.5	0.137
OAD, n (%) OAD+Insuline, n (%) Insuline, n (%)	38 (%76) 8 (%16) 4 (%8)	38 (%76) 8 (%16) 4 (%8)	0.830

*p<0.05 statistical significance,n: number, BMI; body mass index, CAD; coronary artery disease, COPD; chronic obstructive pulmonary disease, CRD; chronic renal disease, HbA1c; glycated haemoglobin A1c, HT; hypertension; OAD; oral anti-diabetic, T2DM; type 2 diabetes mellitus

Table 2. HRV and HRT analysis of study groups

Variables	HT-T2DM+ (n=50)	HT+T2DM+(n=58)	P value
Heart rate, beats/min	78±1.07	76±0.85	0.658
SDNN, ms	113.6±1.68	103.7±2.5	0.002*
SDNN index, ms	44.04±1.6	40.79±1.6	0.166
SDANN, ms	103.2±2.1	95.1±2.3	0.014*
RMSSD, ms	26.8±0.94	24.2±1.1	0.072
pNN50, %	19±1.1	20.4±1.4	0.456
Triangular index	30.6±1.02	29.4±1.01	0.391
Turbulence onset, %	-1.15±0.13	-0.91±0.12	0.202
Turbulence slope, ms/RR	6.35±0.45	5.64±0.42	0.238

pNN50: The proportion of NN50 divided by the total number of NN (R-R) intervals. RMSSD: Root mean square of successive RR interval differences, SDANN: Standard deviation of the average NN intervals for each 5 min segment of a 24 h HRV recording, SDNN: Standard deviation of the NN intervals, *p<0.05 statistical significance

(18). In another research by Bassi et al., similarly, HT + T2DM patients had a significant deterioration in HRV parameters compared to the non-HT group (19). When the literature data and our results are evaluated together, it is seen that the addition of HT to T2DM causes a significant deterioration in HRV parameters compared to the non-hypertensive group. Our results may help to explain why the cardiovascular risk is higher in this group.

Abnormal HRT parameters are detected in patients with autonomic dysfunction and impaired baroreceptor sensitivity. Abnormalities in HRT parameters are also associated with all-cause death and sudden death in patients with post- infarction and heart failure (20). HRT parameters were evaluated separately in both HT and T2DM in different studies and it was shown that there was a deterioration in HRT parameters, more prominent with the progression of the related disease, and it was also associated with cardiac autonomic nervous system dysfunction (21,22). Also, Yosuke et al. reported that HRT measurement in post-infarction DM patients can predict cardiac mortality (23). As far as we know, there is no study in the literature evaluating hypertensive diabetic patients with HRT. Our study is probably the first in which these patients were evaluated with both HRV and HRT. Although HRT values were lower in hypertensive diabetics, the difference between the groups was not significant. While there is no significant difference in HRT values, the decrease we found in HRV parameters (SDNN and SDANN) in the hypertensive diabetes group may indicate cardiac autonomic neuropathy in these patients. Likewise our findings should be scrutinized, particularly with more extensive and long-term research.

Conclusion

In summary, this study's results show that patients with both diabetes and hypertension have higher risk for decreased HRV parameters, but this distinction was not observed in HRT parameters. Early evaluation of the autonomic nerve function is hence advised in diabetic patients with hypertension. Our findings indicate that HT further deteriorates HRV in diabetics, despite the fact that a healthy group was not assessed in this study. Monitoring HRV parameters, which evaluate the regulation of the autonomic nervous system and its response to stimuli, provides insight into the autonomic nervous system of the patients, and could provide leading information for treatments targeting the autonomic nervous system in hypertensive diabetic patients. Future studies are warranted to explore if HRT parameters can be used for patients with hypertensive diabetic and how they are affected. Finally, our observations may have important contributions to the risk reduction strategies.

DECLARATIONS

Conflict of interest: The authors declare that they have no conflict of interest.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Financial Support: No competing financial interests exist.

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Authors contribution:

Concept and design of article: SAY, ZY; Data Collecting: SAY, ZY; Writing: SAY, ZY; Drafting and critical revision of the article: SAY. All authors read and approved the final version of the manuscript.

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Original Article

A Comparative Analysis of English and Turkish Hashtags on Allergic Rhinitis

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ABSTRACT

Background: In an era where social media serves as a powerful medium for information dissemination and interaction, this study focuses on examining and comparing social media hashtags in the English and Turkish languages related to allergic rhinitis on Instagram.

Method: The investigation includes an analysis of the number of followers associated with these hashtags and the extent of their alignment with allergic conditions and the property of the information about allergy according to the Global Initiative for Asthma (GINA) 2023. The study period ranged from January 11, 2022, to April 15, 2023, during which posts tagged with #Allergicrhinitis (English) and #Allerjikrinit (Turkish) on Instagram were meticulously investigated.

Results: The study reveals that the median follower count for #Allerjikrinit and #Allergichinitis hashtags were 4971 (200-231,000) and 469 (130-2321), respectively, with a significant portion of posts (35.2% to 47.8%) being unrelated to allergic rhinitis. The prevalence of advertisements was notably high, with 90% of #Allerjikrinit profiles and 55.7% of their posts containing promotional content. Remarkably, a considerable percentage (75%) of allergy-related information shared in posts contradicted the Global Initiative for Asthma (GINA) 2023 guidelines. Interestingly, 15% of those sharing content were medical professionals, demonstrating the potential influence of healthcare experts on social media platforms.

Conclusion: This study underscores the need for accurate medical information on social media, particularly with the active participation of medical specialists and regulatory institutes given allergic rhinitis since the majority of videos are unrelated to the topic.

Keywords: Social media, allergic rhinitis, instagram, health information, medical professionals

INTRODUCTION

In the current digital age, the integration of social media into daily life has revolutionized the way people access, share, and interact with information (1). Social media platforms have become powerful channels for disseminating a wide range of content, including health-related information with ethics concerns (2).

Allergic rhinitis, characterized by symptoms such as sneezing, nasal congestion, and itching, affects a substantial portion of the global population (3). With the surge in internet penetration and the prevalence of social media use, individuals are increasingly turning to online platforms for health-related queries and discussions (4). This paradigm shift presents both opportunities and challenges, as the democratization of information empowers users to access a wealth of medical content, but also exposes them to potential misinformation and unverified claims.

Instagram, a leading visual-centric social media platform, has emerged as a notable player in this ecosystem, facilitating interactions through images, videos, and hashtags (5). By enabling users to share

personal experiences, insights, and recommendations, Instagram has cultivated a vibrant healthcare-related discourse (6,7). As such, it serves as an ideal platform for examining the prevalence, accuracy, and impact of health-related content, such as allergic rhinitis discussions.

This study undertakes a comprehensive investigation into this phenomenon, with the primary objective of shedding light on the intricate dimensions of allergic rhinitis discourse within the Instagram community. The examination meticulously analyzes the utilization of two distinct hashtags: the English hashtag #Allergicrhinitis and its Turkish equivalent, #Allerjikrinit. This two-fold language approach not only facilitates a cross-cultural comparative analysis but also deepens our insights into the intricate dynamics of information dissemination and consumption across diverse linguistic contexts.

METHODS

Data Collection: The most popular social media applications in our country are youtube, instagram, facebook, twitter and tiktok. Health providers use youtube for verbal information, and instagram accounts for text and visuals. we have done our work on those who use the instagram account that shares the most text and visual content. The study was conducted from January 11, 2022, to April 15, 2023. During this period, Instagram posts tagged with the hashtags #Allergicrhinitis in English and #Allerjikrinit in Turkish were systematically collected for analysis. The selection of hashtags allowed for the inclusion of posts related to allergic rhinitis across two distinct linguistic domains.

Data Analysis: The analysis encompassed two key dimensions: the follower count associated with each hashtag and the alignment of posts with the theme of allergic rhinitis.

Content Classification: Posts were categorized as relevant if they contained content directly related to allergic rhinitis symptoms, treatments, experiences, or awareness. Posts that did not pertain to allergic rhinitis or were unrelated were categorized as non-relevant. 25 unreal Instagram accounts and 30 Instagram accounts that have not shared anything for the last 1 year were not included in the study. Real account holders who regularly post about allergic rhinitis were included in the study.

Accuracy Assessment: In order to assess the accuracy of information shared within relevant posts, each piece of content was cross-referenced with the Global Initiative for Asthma (GINA) 2023 guidelines (8).

Profiling and Commercial Presence: Profiles sharing posts under the hashtags were scrutinized to identify any commercial presence, including advertisements or affiliations with medical entities, pharmaceutical companies, or healthcare-related organizations. Additionally, the involvement of healthcare professionals in sharing content as identified.

All participants completed an informed consent form, the study was carried out in accordance with the Declaration of Helsinki, and it was authorized by the institutional local ethics committee.

RESULTS

The analysis of hashtag follower counts revealed distinct patterns between the English and Turkish hashtags. The median follower count for #Allerjikrinit was 4971 (range: 200-231,000), whereas #Allergicrhinitis garnered a median follower count of 469 (range: 130-2321). In terms of post relevance, a notable proportion of posts were found to be unrelated to allergic rhinitis. Specifically, for #Allerjikrinit, posts ranging from 35.2% to 47.8% were not related to the theme (p= .071), mirroring a similar trend for #Allergicrhinitis. Among profiles sharing under the #Allerjikrinit hashtag, a significant 90% included advertisements in their profiles, and 55.7% of their posts contained promotional content. A diverse array of advertisements emerged, including non-pharmacological treatments (33%), household products (10%), medical devices (3%), and medical services (2%) (Table 1).

Table 1. Distribution of posts according to various parameters

	#Allerjikrinit	#Aller-gicrhi-nitis	P value
Followers, n	4971 (200-231.000)	469 (130-2321	<0.001
Nonrelavent to Allergic Rhinitis	35.2%	47.8%	0.071
Advertisement on Profile	90%	40%	<0.001
Advertisement on posts	55.7%	24.4%	<0.001
Medical information, informative posts-to-noninformative posts, ratio	33.6%	20%	0.049
The accuracy of informative posts	15.4%	45.7%	0.020

Strikingly, around 40% of posts contained allergy-related information. However, an alarming 75% of this information contradicted the Global Initiative for Asthma (GINA) 2023 guidelines, reflecting a substantial discrepancy between shared content and established medical guidelines. Approximately 15% of content contributors were identified as medical professionals.

DISCUSSION

This study demonstrates most of the content on Instagram is not accurate considering allergic rhinitis and should be carefully evaluated by followers. The variability of

the content may be different according to the hashtag's language. The local authorities including relevant professionals on the topic, should take responsibility for controlling and preventing the dissemination of disinformation in this regard.

The high prevalence of non-allergic rhinitis-related posts under both hashtags raises questions about the focus and accuracy of the content shared on Instagram (9). The substantial presence of advertisements, with a variety of non-pharmacological treatments, household products, and medical services, underscores the commercial nature of a significant portion of posts. This commercial influence necessitates cautious evaluation, as misleading or potentially harmful information can inadvertently gain prominence in the guise of expert advice (9,10).

One of the most concerning findings is the substantial mismatch between shared content and established medical guidelines. The presence of misleading or inaccurate information within a majority of posts calls for critical intervention to ensure that health-related discussions on Instagram are grounded in evidence-based practices (4). The discrepancies indicate a pressing need for both healthcare professionals and regulatory bodies to play an active role in guiding accurate health information sharing on social media platforms. With percentages of non-relevant posts ranging from 35.2% to 47.8%, the study highlights a concerning prevalence of irrelevant content within the discourse. Furthermore, the significant presence of advertisements on both profiles and posts underlines the commercial nature of a considerable portion of the content. This commercial influence poses a challenge, as it can blur the line between genuine health information and marketing messages. The data in Table 1 emphasizes the disparity in the accuracy of informative posts given GINA 2023 guidelines (8). The study reveals that only 15.4% of informative posts were accurate for #Allerjikrinit, while this percentage was significantly higher at 45.7% for #Allergicrhinitis. The discrepancy points between the hashtags in English and in Turkish also may indicate the differences in followers' sociocultural and ethnic features. The health-related content on Instagram needs improved fact-checking and source verification mechanisms on social media platforms, to ensure that accurate and reliable information reaches users. The observed inconsistency with medical guidelines signifies the challenges posed by the credibility and accuracy of the information available to users.

The participation of medical professionals in sharing content on allergic rhinitis is a notable aspect of this study. While the engagement of healthcare experts contributes to the authenticity of discussions, the study's findings also indicate a concerning prevalence of inaccuracies within the content shared by medical professionals. This observation emphasizes the importance of continuous medical education and professional accountability, even within the context of social media interactions.

The study's insights have far-reaching implications for both the healthcare community and social media platforms. Strengthening the collaboration between healthcare professionals and regulatory bodies could yield more reliable health content on Instagram. The platform itself can also play a pivotal role in promoting accurate information through algorithmic prioritization of validated sources and fact-checking mechanisms.

Günaydın FE et al. by; In the study conducted by examining Youtube videos using the keyword "asthma", health pros' videos were of the highest quality, but considering the rates of follow-up, alternative medicine is the most videos were watched. Similar to our study, it was determined that the shares of health professionals contained more accurate information (11).

Aydin MF et al. In their youtube study on gastroesophageal reflux disease, it was determined that the posts made by experts in their field contain more accurate information than other posts, and most of the information given by people who are not experts in their field or for advertising purposes were found to be wrong. Their results were similar to our study (12).

Gonzalez-Estrada A et al. In a study conducted on the 200 most watched videos by searching YouTube using the keyword "Asthma", it was found that health care providers got the highest score in terms of quality of their videos, while other servers offered unclear treatments related to alternative medicine, which were far from scientific (13).

Limitations

Several limitations should be acknowledged. The study's focus on Instagram might not capture the entire spectrum of allergic rhinitis discussions across diverse social media platforms. Additionally, the reliance on hashtags as a representation of allergic rhinitis content might overlook posts that are not adequately tagged.

CONCLUSION

In conclusion, this study underscores the dynamic interplay between social media and healthcare, particularly within the context of allergic rhinitis. The findings emphasize the need for vigilant monitoring, accurate content dissemination, and the active engagement of medical professionals and regulatory bodies to ensure the quality and reliability of health-related discussions on platforms like Instagram. By fostering a more informed and trustworthy digital health environment, we can harness the potential of social media for the betterment of public health and medical discourse. Social media users can get the most accurate information about allergic rhinitis on

Instagram from healthcare providers who are experts in allergy. Most of the posts made by alternative medicine, pharmaceutical companies and non-experts do not provide accurate information.

DECLARATIONS

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Original Article

Prognostic Value of Systemic Immune Inflammation Index in Malignant Ischemic Stroke: A Study on Patient Selection and Timing of Surgical Decompression

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ABSTRACT

Background: Ischemic stroke is a substantial health concern with long-term neurological consequences and economic implications. Inflammation worsens secondary brain injury, prompting the search for prognostic biomarkers. The optimal approach for treating malignant ischemic stroke, patient selection, and intervention timing remain intricate due to patient diversity.

Methods: We investigate the systemic immune inflammation index (SII) predictive value for surgical decompression timing and patient selection in malignant ischemic stroke. We include patients who underwent surgical decompression for ischemic stroke-induced malignant brain edema in the past five years. Retrospective data were collected, including demographics, history, laboratory results, imaging, and surgical details. SII was calculated using platelet, neutrophil, and lymphocyte counts. Descriptive statistics and multivariate regression models were used.

Results: In this study involving 80 patients, we evaluated the impact of decompressive craniectomy on ischemic stroke outcomes. Patients were divided into the Decompression Group (n=39) and Non-Decompression Group (n=41). Gender distribution, hypertension, diabetes mellitus, atrial fibrillation, and hemorrhage occurrence showed no significant differences between the groups. However, the Decompression Group had higher NIHSS scores at presentation (18.1±4.6 vs. 14.8±4.7, P=0.02) and discharge (17±5 vs. 11.2±4, P=0.001). SII at presentation and control were significantly higher in the Decompression Group (P=0.04 and P=0.05, respectively). Hospitalization duration on the 10th day was longer in the Decompression Group (39.5±28.8 vs. 11.8±5.6, P=0.001).

Conclusions: Our study examines SII's potential as a prognostic marker for surgical decompression timing and patient selection in malignant ischemic stroke. Despite limitations, we highlight the complex relationship between systemic inflammation, stroke severity, and post-surgical outcomes. Further research with larger cohorts must validate SII's utility and refine its application in ischemic stroke management. Continued investigation is crucial to establish SII's role as a predictive tool in guiding clinical decisions.

Keywords: Decompressive craniectomy, ischemic infarct, malign cerebral edema, systemic immune inflammation index

INTRODUCTION

Ischemic stroke, particularly occlusive ischemic stroke, represents a severe health concern beyond a life-threatening condition, often leading to permanent neurological disabilities and affecting a broad spectrum of society. This challenging scenario exerts detrimental impacts not only on individuals' quality of life but also on the societal economic equilibrium.

Ischemic stroke is characterized by inflammation as a pivotal contributor to its pathology and outcome. Inflammation exacerbates secondary brain injury by deteriorating the blood-brain barrier, compromising microvascular function, inducing brain edema and oxidative stress, and directly causing neuronal cell death (1,2). This recognition has prompted the exploration of inflammation as a primary target for advancing

novel stroke therapies. Among the goals is utilizing inflammatory biomarkers to enhance mortality prediction and functional outcomes in stroke patients.

Despite advancements, the existing options for acute ischemic stroke treatment remain limited and costly. The queries of which treatment approaches to apply, when, and for whom continue to lack comprehensive answers. Notably, in the case of malignant ischemic stroke, selecting appropriate candidates and optimal timing for interventions such as surgical decompression pose challenges (3-5). These challenges are compounded by the heterogeneous nature of stroke patients, characterized by diverse demographic profiles and comorbidities.

Various inflammatory indicators, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and red blood cell distribution width (RDW), have been investigated as potential prognostic markers in ischemic stroke (6-7). However, their predictive values have shown inconsistent levels of significance. A newly emerging inflammatory index, known as the Systemic Immune Inflammation Index (SII), is calculated by combining three immune-inflammatory cell types (lymphocytes, neutrophils, and platelets), providing a comprehensive reflection of the inflammatory status (8). Elevated SII levels have been shown to increase the risk of stroke in hypertensive patients and impact the prognosis of these patients (9). Based on these findings, the purpose of our study was to calculate SII based on the initial routine blood test at the time of admission and SII obtained from the blood test during neurological deterioration in patients presenting with acute large vascular occlusion that subsequently develops malignant cerebral edema. We aimed to establish a model for predicting the requirements of decompressive craniectomy (DC) and further validate the predictive value of SII in estimating the prolonged prognosis of patients who undergo DC treatment.

METHODS

Study Design

The study aims to investigate the prognostic utility of the SII in determining the optimal timing for DC and selecting suitable patients with malignant brain edema resulting from ischemic stroke.

Data Source and Patient Selection

Patients in our hospital within the last five years who developed malignant brain edema after ischemic stroke and patients who underwent DC due to malignant brain edema will be included in the study. Patient data will be derived from electronic health records, surgical reports, and medical imaging studies. The data collection process will be retrospective and include demographic information, medical history, laboratory results, imaging findings, and surgical details.

Patient Management: The AHA-ASA standard protocol for acute ischemic stroke treatment (10) was administered in patients displaying clinical symptoms of acute ischemic stroke. Upon admission, all patients underwent Brain Computed Tomography (CT) or, in suitable cases, CT angiography. Patients with symptom onset within the first 4.5 hours and no contraindications received intravenous thrombolysis; those with treatable large vessel occlusion within the first 6 hours after symptom onset, according to CT angiography, were subjected to endovascular treatment All 80 patients received standardized conservative management, including measures such as controlling blood pressure, administering hyperosmolar treatment, utilizing hypertonic saline solutions, and implementing hyperventilation techniques. Following confirmation of space-occupying hemispheric infarction on follow-up CT, similar to the HAMLET (11) study protocol, DC was performed when the Glasgow Coma Scale (GCS) score dropped to ≤13 for right hemispheric lesions or ≤9 for left-sided lesions. There was no strict time limit of 48 hours between stroke onset and DC. Other HAMLET exclusion criteria, such as age >60, hemorrhagic transformation, and involvement of other vascular territories, were not applied; a neurologist and a neurosurgeon discussed the clinical course and overall condition of such patients, and the decision regarding DC was made after obtaining informed consent from the patient and their family.

During DC, a large skin incision was made in the shape of a question mark based on the ear base. Subsequently, a bone flap containing frontal, temporal, and parietal bones with a diameter of at least 120 mm was created. The craniectomy was extended to the temporal skull base. The dura was opened widely in a cross-shaped manner. The cortical surface was covered with non-approximated dural flaps and absorbable hemostatic cellulose. Finally, the skin was closed. Postoperatively, all patients were admitted to the Intensive Care Unit (ICU) for supportive care purposes.

Calculation of Systemic Immune Inflammation Index (SII): SII was calculated by multiplying the platelet (P) count by the neutrophil (N) count and then dividing the result by the lymphocyte (L) count (SII = P x N/L), with platelet, neutrophil, and lymphocyte counts extracted from laboratory results.

STATISTICAL ANALYSIS

The study data were analyzed in SPSS (Statistical Package for the Social Sciences) 23.0 and MedCalc 23.110. Numeric data were expressed as median (interquartile range (IQR)) and frequent data as rates. Comparison of two independent groups with numeric data was carried out by Mann Whitney U test, and the Chi-square test was used for frequent data. The Kolmogorov-Smirnov test conducted the normality analysis. Logistic regression

Table 1. Characteristics of the patients at baseline

Variables	Decompression Group (n=39)	Non-decompression Group (n=41)
Age, years	71 (67 to 75)	75 (69 to 80)
Gender, n Female Male	 13 (33.3) 26 (66.7)	 21 (51.2) 20 (48.8)
Hypertension, n	31 (79.5)	28 (68.3)
Diabetes Mellitus, n	12 (30.8)	17 (41.5)
Atrial Fibrillation, n	22 (56.4)	16 (39)
Hemorrhage, n	16 (41)	19 (46.3)
NIH Stroke Scale	18 (15 to 22)	14 (11 to 18)
NIH Stroke Scale Mild (1-10) Moderate (1-18) Severe (≥19)	 2 (5.1) 19 (48.7) 18 (46.2)	 9 (22) 22 (53.7) 10 (24.4)

SII; systemic immune-inflammation index; IQR; interquartile range *Data are expressed as n (%) and median (IQR) unless otherwise stated.

analysis was used for multivariate analysis to ascertain the independent variables predicting the 3rd month mortality. All the hypotheses were constructed as two-tailed, and an alpha critical value of 0.05 was accepted as significant.

RESULTS

Baseline Characteristics of Patients: **Table 1** presents the baseline characteristics of patients in the Decompression Group (n=39) and the Non-decompression Group (n=41). The Decompression Group had a median age of 71 years (IQR: 67 to 75), while the Non-decompression Group had a median age of 75 years (IQR: 69 to 80). Gender distribution showed that most patients in the Decompression Group were male (66.7%), whereas the Non-decompression Group had a slightly higher proportion of females (51.2%). The prevalence of comorbidities such as hypertension, diabetes mellitus, atrial fibrillation, and hemorrhage varied between groups. Notably, the median NIH Stroke Scale score at baseline was higher in the Decompression Group (18, IQR: 15 to 22) compared to the Non-decompression Group (14, IQR: 11 to 18).

Primary and Secondary Outcomes: **Table 2** outlines both groups' primary and secondary outcomes. Mortality in the third month was significantly higher in the Decompression Group (38.5%) compared to the Non-decompression Group (17.1%), with a p-value of 0.03. Additionally, the Modified Rankin Scale (mRS) score was higher in the Decompression Group (median: 5, IQR: 4 to 6) than in the Non-decompression Group (median: 4, IQR: 3 to 5), with a p-value of 0.00. Hospitalization duration was notably longer in the Decompression Group (median: 29 days, IQR: 19 to 56) compared to the Non-decompression Group (median: 10 days, IQR: 8 to 14). Moreover, NIH Stroke Scale scores at discharge were also higher in the Decompression Group (median: 18, IQR: 13 to 20) than in the Non-decompression Group (median: 12, IQR: 9 to 14), with p-values of 0.00.

Table 2. Primary and secondary outcomes in decompression and non-decompression groups

Variable	Decompression Group (n=39)	Non-decompression Group Value (n=41)	P value
Mortality*	15 (38.5)	7 (17.1)	0.03
mRS	5 (4 to 6)	4 (3 to 5)	0.00
SII control	887 (487 to 1190)	950 (504 to 1206)	0.55
Hospitalization (days)	29 (19 to 56)	10 (8 to 14)	0.00
NIH Stroke Scale (at discharge)	18 (13 to 20)	12 (9 to 14)	0.00
SII Difference	19 (-516 to 278)	39 (-328 to 531)	0.40

SS; standard deviation; NIH Stroke Scale; SII; systemic immune-inflammation index
*Mortality in the 3rd month, ^Data are expressed as n (%) and median (IQR) unless otherwise stated

Table 3. Univariate comparison of patients with and without mortality at the 3rd month regarding the co-morbidities, NIHSS and systemic immune-inflammation index

Variable	Mortality (n=22)	No Mortality (n=58)	P Value
Age, years	75 (68 to 77)	71.5 (68 to 75)	0.49
Diabetes Mellitus, n	9 (40.9)	20 (34.5)	0.59
Hypertension, n	16 (72.7)	43 (74.1)	0.89
NIH Stroke Scale*	19.5 (16 to 24)	15 (11 to 18)	0.00
SII*	1019 (663 to 1347)	693 (458 to 1209)	0.22
SII difference	-209.7 (-357 to 100)	130.4 (-213 to 522)	0.01

SS; standard deviation; NIH Stroke Scale; SII; systemic immune-inflammation index
*NIH Stroke Scale and SII at presentation, ^Data are expressed as n (%) and median (IQR) unless otherwise stated.

Table 4. Logistic regression analysis in order to establish the independent variables predicting mortality at the 3rd month

Variable	Odds Ratio	95% CI	P Value
Age	0.96	0.9 to 1.3	0.29
Diabetes Mellitus	3.7	0.9 to 16	0.07
NIH Stroke Scale	1.4	1.17 to 1.7	0.00
SII at presentation	1	0.99 to 1	0.40
Hemorrhage	5	1.24 to 20	0.02
Hypertension	0.67	0.15 to 3	0.60
Decompression	1.68	0.4 to 7	0.47

CI; confidence interval; SII; systemic immune-inflammation index

Univariate Comparison of Mortality: **Table 3** explores the univariate comparison of patients with and without mortality in the third month. Age, comorbidities (diabetes mellitus and hypertension), baseline NIH Stroke Scale scores, systemic immune-inflammation index (SII) at presentation, and SII difference were assessed. Notably, patients who experienced mortality had significantly higher baseline NIH Stroke Scale scores (median: 19.5, IQR: 16 to 24) than survivors (median: 15, IQR: 11 to 18) with a p-value of 0.00. The SII difference was also significantly different between the two groups (p-value: 0.01).

Logistic Regression Analysis: Table 4 presents the logistic regression analysis results to identify independent variables predicting mortality in the third month. The analysis revealed that higher baseline NIH Stroke Scale scores (Odds Ratio: 1.4, 95% CI: 1.17 to 1.7) and the presence of hemorrhage (Odds Ratio: 5, 95% CI: 1.24 to 20) were associated with increased odds of mortality. However, decompression did not significantly influence mortality (Odds Ratio: 1.68, 95% CI: 0.4 to 7).

These results suggest that baseline stroke severity, as measured by the NIH Stroke Scale and the presence of hemorrhage are significant predictors of mortality in the third month. At the same time, the choice of decompression did not independently impact mortality outcomes.

DISCUSSION

In recent years, studies focusing on the post-stroke inflammatory response have steadily increased. It is believed that inflammation plays a role in initiating post-stroke recovery and repair processes, but certain aspects of the inflammatory response in stroke patients can have detrimental effects (12). A novel inflammatory index, SII, is calculated by combining three immune-inflammatory cell types (lymphocytes, neutrophils, and platelets), comprehensively reflecting the inflammatory status (8). Elevated SII levels have been shown to increase the risk of stroke in hypertensive patients and impact the prognosis of these patients (9). Therefore, the purpose of our study was to calculate SII based on the initial routine blood test at the time of admission, establish a model for predicting the requirements of DC, and validate the predictive value of SII to aid in selecting patients for DC.

Treating patients with malignant cerebral edema following ischemic stroke remains quite challenging. Decompressive craniectomy can reduce brain herniation and prevent death by reducing the mass effect on infarcted brain tissue (13). The current consensus suggests that after identifying brain herniation through imaging, DC can be performed as soon as possible without waiting for neurological deterioration (14). Various studies have shown that decompressive surgery can reduce the mortality rate from 80% to 30% in cerebral edema following ischemic stroke cases. Oliver and colleagues suggested that monitoring the optic nerve sheath diameter with ultrasound in patients with large vessel occlusion could predict severe intracranial hypertension and help select appropriate candidates for DC (15). However, it is still unclear which patients with extensive middle cerebral artery occlusion will develop severe cerebral edema necessitating decompressive surgery or which group will benefit the most from the procedure. Given the long-term effects of chronic physical disability and psychosocial problems following DC in treating ischemic stroke-related malignant cerebral edema, it is challenging to decide which patients are suitable for early or preventative surgery or to defer surgery until clear evidence of improvement or deterioration emerges. Over the past few years, an increasing number of studies have highlighted the significance of inflammation in the pathogenesis of ischemic stroke (16,17). Inflammatory pathways activated during acute and reparative stages of ischemic stroke involving cytokines, chemokines, and damage-associated molecular patterns play a crucial role in tissue damage and prognosis after ischemic stroke (18). The pro-inflammatory signals arising from endothelial and cerebral tissue damage within minutes of cerebral ischemia can exacerbate brain damage by influencing the infiltration of various inflammatory cells (neutrophils, monocytes/macrophages, different subtypes of T cells, and other inflammatory cells) into the ischemic region (19). Studies have shown neutrophils are the first cells to respond to cerebral ischemia (20). Neutrophils, part of the innate immune system, can intensify brain parenchymal inflammation by activating numerous pro-inflammatory cytokines. Inflammatory reactions following neutrophil endothelial adhesion can damage secondary brain tissue (21,22).

Additionally, cerebral ischemia and hypoxia can induce monocytes to produce inflammatory mediators like interleukin-6 (IL-6) and tumor necrosis factor (TNF), further exacerbating secondary injury after cerebral ischemia and hypoxia, aggravating comprehensive brain tissue damage, and suggesting that the detrimental effects of white blood cells are not limited to neutrophils (23). Platelet-monocyte aggregates (PMA) formed by

monocyte activation of platelets following ischemic brain injury contribute to vascular thrombosis and occlusion, intensifying post-ischemic inflammation by releasing vasoactive mediators and worsening ischemia (24). Given the complex nature of inflammation, simply counting the number of white blood cells is insufficient to indicate the severity of inflammation. Therefore, new biomarkers have been designed by combining different subtypes of white blood cells, such as the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), SIRI, or SII, based on various inflammatory parameters associated with stroke (25,26). For example, Zhang and colleagues investigated the impact of the systemic inflammatory response index (SIRI) on prognosis in patients with acute ischemic stroke, finding a positive correlation between NLR and three-month mortality risk and an independent association between low lymphocyte-monocyte ratio and increased risk of hemorrhagic transformation in stroke patients (27).

The newly introduced SII, calculated by combining three immune-inflammatory cell types (lymphocytes, neutrophils, and platelets), comprehensively reflects the inflammatory status (8). Previous studies have reported that SII predicts prognosis in myocardial infarction, breast cancer, and small-cell lung cancer patients (28,12). Luo and colleagues included 76 patients with aneurysmal subarachnoid hemorrhage in their prognostic analyses, showing that SII at admission was closely related to their six-month clinical outcomes (29). Chen and colleagues (30) also demonstrated that SII was an independent predictor for delayed cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage. In our study, SII calculated from the admission blood test was significantly lower in patients with malignant ischemic stroke who experienced neurological deterioration. This situation suggests that changes in SII in ischemic malignant cerebral edema could be a predictive parameter for DC.

Results from studies have indicated that biomarkers related to systemic inflammation are associated with the development of malignant cerebral edema and all-cause mortality following acute ischemic stroke (27). However, no data in the literature shows the contribution of high SII during acute ischemic stroke and increasing SII values during follow-up to the development of malignant cerebral edema and their relevance in the selection of the appropriate patient group for DC. Our study observed that increased SII in the first days of middle cerebral artery occlusion-related ischemic stroke was strongly associated with malignant cerebral edema development and mortality in patients who underwent decompression.

It is widely accepted that the higher the NIHSS score, the more severe the stroke is. In our study, there was a positive correlation between SII and NIHSS; based on these findings, it can be concluded that there is a positive correlation between SII and stroke severity. As far as we know, no study has previously documented the role of SII in stroke prognosis. Therefore, there is great potential to use SII to predict stroke prognosis.

The Study Limitations

1. The subjects in this study were selected from a single center, which may have led to selection bias or geographically biased results. The next step would be to conduct a multi-center study.
2. The number of standard variables related to stroke prognosis was extraordinarily high and collected quately in our study. More data on other parameters are required to enhance the robustness of our results.
3. The sample size in our study was relatively small; larger sample sizes are needed to confirm our findings.

CONCLUSION

Our study contributes to the growing body of literature elucidating the intricate relationship between systemic inflammation biomarkers, stroke severity, the development of malignant brain edema, and post-surgical outcomes. Further research, incorporating larger samples and broader variables, is warranted to validate the utility of SII as a prognostic tool and to refine patient selection criteria for decompressive surgery in ischemic stroke. Our findings underscore the potential of SII to aid in predicting outcomes and guiding clinical decision-making. However, continued investigation is imperative to cement its role in the stroke management paradigm.

DECLARATIONS

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Ethical Considerations: We secured ethical approval from the institutional review board (Health Sciences University Antalya Training and Research Hospital Clinical Research Ethics Committee, Approval Number and date: 11/24, 24/08/2023). Informed consent was waived due to the retrospective nature of the study. This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subjects.

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Original Article

Comparison of Peritoneal Catheter Insertion Techniques: A Single-Center Experience Comparing Percutaneous and Laparoscopic Approaches

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ABSTRACT

Background: There is still no consensus on the best approach for the insertion of the peritoneal dialysis catheter. We aimed to compare the results of the percutaneous Sildenger and laparoscopic surgical peritoneal dialysis catheter insertion approaches.

Materials and methods: The study examined the files of patients in the chronic PD program retrospectively. Demographic characteristics such as early and late complications, attacks of infection, time of use of the catheter, and number of hospitalizations were recorded to compare both methods. (Tablo 1). The results were evaluated through appropriate statistical analysis of the data.

Results: In our study, 32 (53.3%) out of 60 patients included were males. Patients were divided into two groups, the percutaneous PD catheter group (Group 1, n=36) and the Laparoscopic PD catheter group (Group 2, n = 24). The average age for group 1 was 65 years, while it was 57 years for group 2 (p = 0.197). The median follow-up time of the study population was 17 months (7-41). The average first usage time of the PD catheter was 13.5 (11-16.5) days in group 1 versus 21.5 (18.5-27.5) days (p 0.001) in group 2. The exit site leak was 11.1% (n = 4) versus 33.3% (n = 8) in groups 1 and 2, respectively (P = 0.039). No significant difference was observed between the two groups in terms of hospitalization, renal replacement treatment transition, and death.

Conclusion: The percutaneous approach for PD catheter insertion is more advantageous compared to surgical techniques with fewer complications. More importantly, there is no risk of anesthesia, in addition to shorter incisions and less hospitalization time.

Keywords: Decompressive craniectomy, ischemic infarct, malign cerebral edema, systemic immune inflammation index

INTRODUCTION

Peritoneal dialysis (PD) is one of the best options offered to patients with end-stage renal disease. We need a safe and long-lasting tool for this treatment option's successful and long-standing utilization. The success of PD as renal replacement therapy (RRT) depends on a well-functioning peritoneal catheter. Knowledge of best practices in catheter insertion can minimize the risk of catheter complications that lead to PD failure. Peritoneal catheter types and insertion techniques have evolved over time. Many techniques and insertion sites were tried for safe insertion and the least complications (1-7). The main aim is always to attain maximal duration with the least complications. Surgical complications and infections are the major concerns for peritoneal dialysis patients. Technical failure and recurrent peritonitis constitute major reasons for transfer to hemodialysis (8,9). Catheter insertion types include percutaneous with or without image guidance, open surgical dissection, peritoenoscopic, and surgical laparoscopy (10). The Tenckhoff trocar and the Seldinger approach are the two most popular percutaneous procedures (10-12). With the percutaneous approach, the peritoneal dialysis catheter is more easily tolerated, starting PD sooner and requiring

a smaller incision line. Open surgical procedures are replaced with laparoscopic techniques. The laparoscopic approach has fewer complications when compared to the oldest traditional surgical approaches (13). Blind insertion percutaneously was also found to have a comparable complication and safety profile when compared with laparoscopic insertion (14,15). Despite being more advantageous, the laparoscopic technique entails complicated equipment, an operation room, and general anesthesia. On the other hand, the Percutaneous Seldeinger technique is a bedside procedure performed with local anesthesia and does not necessitate complex, expensive equipment. There is no clear-cut consensus regarding the best peritoneal dialysis (PD) catheter placement approach. All procedures have their pros and cons. Previous studies and reports did not exclusively favor one specific technique over another (16). The advantage of the laparoscopic approach over the more traditional open approach has been well documented in many studies (17-19). We aimed to compare the outcomes of Sildenger percutaneous and laparoscopic peritoneal dialysis catheter placement approaches.

METHODS

The present study was conducted on 109 patients followed retrospectively in our peritoneal dialysis outpatient clinic. The study was conducted in accordance with the Declaration of Helsinki and after approval of the ethics committee of our university faculty of medicine (E-71522473-050.01.04-241662-327). The percutaneous PD catheter was inserted by a nephrologist under local anesthesia and prophylactic antibiotics in the intervention room, while the laparoscopic PD catheter was inserted by the same nephrologist with the help of a general surgeon under general anesthesia and prophylactic antibiotics in the operating room. Prior to the procedure, all patients had intestinal cleaning with a fleet enema the day before and 2 hours before the procedure. All received pre-operative prophylactic 1 gram cefazoline antibiotic therapy. Laparoscopic insertion was performed primarily by surgeons with the assistance of a nephrologist in the operating room. Under general anesthesia, a median of 2-3 cm in the sub-abdominal region, with additional holes for laparoscopy, was performed. To prevent organ trauma at this level, 1000 ml of 1.36% glucose dialysis solution (supplemented with 500U/L heparin) was administered through the peritoneal membrane through the 16G intracath. After the PD solution injection, a guide wire was sent, and then the rectal muscle and peritoneal membrane were dilated with a dilatator, and a catheter was inserted in the abdominal cavity. The catheter was placed with direct vision into the Douglas space. For the percutaneous Sildenger method, the same preoperative measures were conducted. After local anesthesia, a left paramedian superficial cut below the umbilicus was performed (1-maximum of 1.5 cm) to allow dilatation using the fifth digit of the right hand of the operating nephrologist. like the surgical method, the peritoneal cavity was rinsed with heparinized dialytic solution (1000 ml of 1.36% solution). All patients had a direct abdominal X-ray (in a standing position). As shown in **Figure 1** (Flowchart), we included 60 patients who were actively followed for the last 5 years (**Table 1**). 3 out of 24 patients in group 2 had an obligatory laparoscopic approach. One because of morbid obesity and the other two because of incompliance. Our inclusion criteria were age over 18, catheter insertion in our institution, and the least follow-up duration of 6 months. We excluded patients with missing data, open surgical techniques, those with short follow-up, and those not performed primarily in our center. Baseline demographic, biochemical parameters, and other items, including primary disease, duration of PD period, residual urine, complications resulting from PD catheter insertion, the time between catheter insertion and first use, discontinuation of the PD program for any reason, and switching to another renal replacement therapy modality. We concluded the study by performing an appropriate statistical analysis of all recorded data.

STATISTICAL ANALYSIS

A descriptive analysis was performed to provide information on the general characteristics of the study population. We used Visual (probability plots, histograms) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk's test) to evaluate the normality of the distribution. The descriptive analyses were presented using the median (IQR, 25th–75th percentile) to compare our non-normally distributed variables. We used the Mann-Whitney U test for nonparametric parameters. The categorical variables were presented as frequency (% percentage). Categorical variables between the two groups were evaluated using the Chi-square test. Automated analyses were performed by SPSS statistics

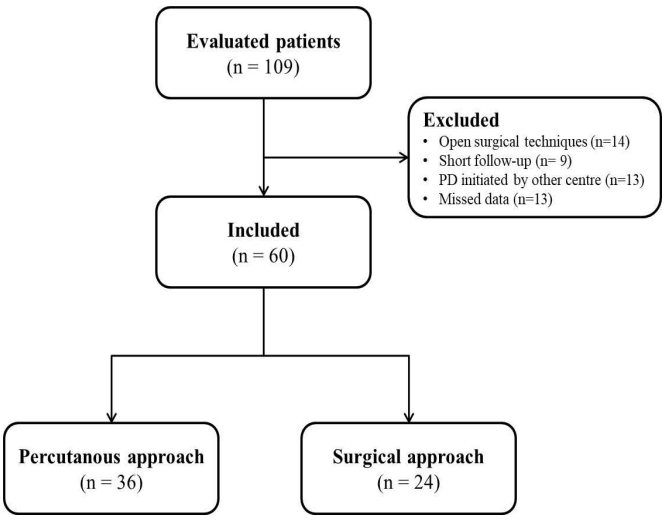

Figure 1. Study flowchart

Table 1. Comparison of demographic and basal characteristics of the study population

	Percutaneous Approach (No= 36) Group 1	Laparoscopic approach (No=24) Group 2	All patients (n=60)	p value
Age, year*	65.0 (17.5)	57 (19)	63.0 (53.0-69.5)	0.197
Sex, (Male), n (%)	20 (55)	12 (50)	32 (53.3)	0.433
BMI, kg/m2*	27.8 (8.5)	30.1 (7.5)	29.0 (8)	0.077
Diyabetes Mellitus, no (%)	8 (22.2)	6 (25)	14 (23.3)	0.520
Hipertansiyon, no (%)	36 (100)	24 (100)	60 (100)	NA
Bazal hemoglobin (g/dl)*	9.3 (1.6)	9.4 (2.6)	9.3 (2.2)	0.651
Basal urea, (mg/dl)*	148.8 (54)	169.7 (38.6)	160.0 (55.3)	0.069
Basal serum creatinine, (mg/dl)*	4.0 (3.3)	4.7 (3.6)	4.1 (4.5)	0.963
Basal sodium, (mmol/L)*	136.0 (7)	137.5 (7)	137.0 (7)	0.639
Bazal potassium, (mmol/L)*	4.2 (1.3)	4.6 (1.1)	4.3 (1.2)	0.141
Assisted PD, n (%)	18 (50)	7 (29.2)	25 (41.7)	0.09
HIV positive, n (%)	0	0	1 (1.17)	1
HBV positive, n (%)	0	0	0	NA
HCV positive, n (%)	0	0	0	NA

* Expressed as median (IQR), BMI; body mass index, IQR; interquartile range PD; peritoneal dialysis

software (IBM SPSS Statistics, Version 21.0). P-value <0.05 was considered significant.

RESULTS

Our study included 60 patients with a mean age of 63 years (53-69.5). 53.3% (n=32) of patients were males. Patients were divided into two groups based on the PD catheter insertion approach. The percutaneous PD catheter group (Group 1) included 36 (60%), and the laparoscopic PD catheter group (Group 2) included 24 (40%). The average age for group 1 was 65 years (53.5-71), while it was 57 years (49-68) for group 2 (p=0.197). As shown in **Table 2**, the median follow-up time of the study population was 17 months (7-41) (**Figure 2** & **Figure 3**). The average first usage time of the PD catheter was 13.5 (11-16.5) days in group 1 versus 21.5 (18.5-27.5) days in group 2 (p<0.001). The exit site leak was 11.1% (n=4) versus 33.3% (n=8) in groups 1 and 2, respectively (P=0.039). No significant difference was observed between the two groups regarding hospitalization, renal replacement treatment transition, and death. As shown in Table 2, while late (> three months), subcutaneous edema was 11.1% (n=4) in group 1, it was 33.3% (n=8) in group 2 (p=0.039). Two patients (8.3%) developed exit-site infection in group 2, while none were in group 1.

DISCUSSION

In the present study, we compared the outcomes of Sildenger percutaneous and laparoscopic peritoneal dialysis catheter insertion approaches, and we found no significant differences between the two modalities in terms of primary endpoints like morbidity, hospitalization, and death ratio. However, we demonstrated some important advantages in favor of the percutaneous PD catheter insertion method, like shorter time to start PD

Table 2. Comparison of outcomes of percutaneous and laparoscopic peritoneal catheter insertion approaches

	Group 1 Percutanous sildenger approach (No= 36)	Group 2 Laparoscopic Approach (No=24)	TOTAL (n=60)	p
Time lapsing untill first use (days), median (IQR)	13.5 (5.5)	21.5 (9)	16 (8.5)	P <0.001
Total followup duration (month), median (IQR)	11 (29.5)	29 (46)	17 (34)	0.006
Subcutaneous edema (first 3 months), n (%)	2 (5.6)	1 (4.3)	3(5.1)	0.665
Exit-site leak (first 3 months), n (%)	4 (11.1)	8 (33.3)	12 (20.0)	0.039
Hemoperitonium, n (%)	7 (19.4)	6 (25)	13 (21.7)	0.420
Hernia, n (%)	5 (13.9)	3(12.5)	8 (13.3)	1
Exit-site infection, n (%)	0 (0.0)	2(8.3)	2 (3.3)	0.079
Catheter malposition, n (%)	7 (19.4)	6 (25.0)	13 (21.7)	0.420
Catheter removal for any cause, n (%)	10 (28.6)	4 (16.7)	14(23.7)	0.230
Hospitalizations, n (%)	14 (40.0)	14 (58.3)	28 (46)	0.309
Transfer to hemodialysis, n (%)	2 (5.6)	2 (8.3)	4 (6.7)	0.528
Transfer to renal transplantation, n (%)	3 (8.3)	1 (4.2)	4 (6.7)	0.472

IQR; interquartile range

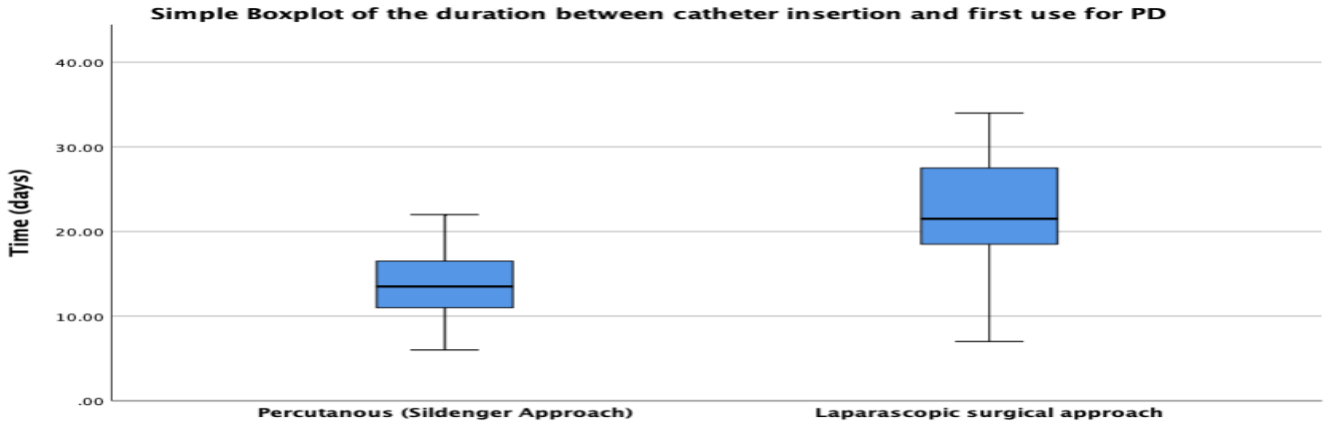

Figure 2. The time between PD catheter insertion and first peritoneal dialysis in days.
The duration between catheter placement and peritoneal dialysis (PD) initiation was shorter in group 1 (Sildenger technique) than in the Laparoscopic surgical approach. Time until the first PD session was 13.5 (11-16.5) days Versus 21.5 (18.5-27.5) days in groups 1 and 2 respectively (P <0.001).

dialysis, lower rates of leakage, and less exit-site or tunnel infection. The absence of need for general anesthesia and operating room are other crucial benefits. The time between PD catheter insertion and PD initiation was significantly shorter in favor of the percutaneous insertion method. ISPD guidelines recommend a break-in period of at least two weeks before elective start on PD (16,20). In our study, despite the mean waiting time of three weeks in the laparoscopic PD catheter insertion group, technical complications were more common.

In terms of exit-site infection and peritonitis, we noted that there was no difference between comparable groups. In the literature, controversial results have been reported in this field (14,15,21-24). In one study, two weeks after catheter placement, catheter-related infection episodes occurred in 13.6% of patients with percutaneous approach versus 14.3% of patients in the laparoscopic insertion group (15). However, in another study, percutaneous PD catheter insertion had a lower relative risk concerning exit-site infection and early peritonitis compared with the surgical approach [64% (95% CI = 47%-76%) vs 48% (95% CI = 23%-64%); respectively] (21). In another study including 121 patients, there was no statistically significant difference regarding complications either in catehteres with survival of more than 12 months as those with survival of less than 12 months (25). Unplanned urgent peritoneal dialysis initiation is a problem in late referred patients and may be a reason for PD catheter-related complications in the early period (26).

Initiation of dialysis following catheter placement should be delayed for two weeks when possible to minimize the risk of leaks. The incidence of exit-site

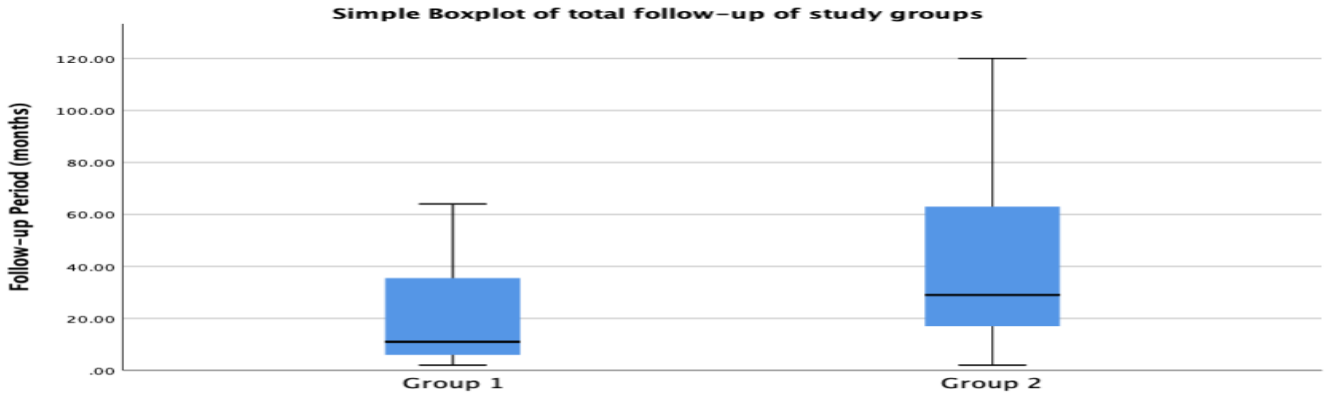

Figure 3. The total time follow-up of the study population.
The total follow-up period was higher in group 2 (surgical method) than in group 1 (Sildenger technique). The median follow-up in group 1 was 11 (6-35.5) months versus 29 (17-63) months in group 2 (P = 0.006). The preferred insertion method is the percutaneous method unless an obligatory reason is indicated. Only 3 patients from group 1 had obligatory laparoscopic insertion. The total follow-up period was higher in group 2 (surgical method) than in group 1 (Sildenger technique). The median follow-up in group 1 was 11 (6-35.5) months versus 29 (17-63) months in group 2 (P = 0.006). The preferred insertion method is the percutaneous method unless an obligatory reason is indicated. Only 3 patients from group 1 had obligatory laparoscopic insertion.

leak rates was higher in the surgical group (%33.3 vs. %11.1). Our results are consistent with other studies (15,21,27). However, according to the results of meta-analyses, there were no significant differences between the percutaneous and surgical methods in terms of excite-side leak (21,28). The main reasons for our leak results in favor of the percutaneous method may be that the team has years of experience, we used the catheter in accordance with the literature (at least two weeks), and we performed the catheter exit site without incision (20). No statistically significant difference was observed in other outcomes, including catheter survival and mechanical complications. These results were consistent with the literature (15,28,29). In another study comparing three different techniques (open surgery, Sildenger, and modified Sildenger), the complication rate of catheter malposition was higher than either procedure (39.1% for sildenger compared to 27.3 % and 9.1 % in open surgical and modified sildenger, respectively) (30). In our study, the rate was 19.4%, which is lower, but the gap is not very high. This may be due to the small sample size, which is 23 in the Ma et al. study compared to 36 in our study (30).

Due to the inherent nature of percutaneous techniques as blind procedures, there exists a minor potential for inadvertent perforation of the abdominal organs. Previous investigations utilizing the percutaneous approach have demonstrated an exceedingly low incidence of perforation, ranging from 0% to 1.3% (31-33). Efforts are made to mitigate the occurrence of this problem by instilling fluid into the abdominal cavity either during or immediately prior to the insertion. This complication has not been observed during any of the catheter procedures performed in our clinic. Y. Koc et al. reported more exit site bleeding complications in the Seldinger technique than in the surgical technique (34). In our study, the exit site bleeding was comparable, and no major problem was documented. This may be due to planned procedures and paying attention to the complete stopping of antiaggregants at least 5 days before the procedure. It is important to note that the use of antiaggregants should always be carefully considered and managed in order to minimize bleeding complications during catheter procedures. Additionally, our study found that both the Sildenger and laparoscopic techniques had a lower incidence of post-procedure bleeding complications compared to the open surgical technique reported in the Y. Koc et al. study (34). This could be attributed to the direct visualization and control of bleeding during the surgical approach. Rather, the incision is smaller in laparoscopic technique and even shorter in our clinical practice. Further research is needed to evaluate this point.

Limitations of the Study

Sample Size: The study's sample size may be relatively small, limiting the generalizability of the findings to a broader population of individuals with CKD observing Ramadan fasting.

Retrospective Data: The study's retrospective nature may introduce inherent biases and limitations in data collection and analysis, potentially affecting the accuracy and completeness of the information obtained. Prospective studies comparing the outcomes, burden of hospitalizations, and costs are needed to clarify superiority.

Single-Center Study: Conducting the study at a single center may limit the diversity of the study population and restrict the representation of individuals treated with peritoneal dialysis from different geographic regions or healthcare settings.

Costs: We did not have accurate calculations to compare the costs of the two methods.

CONCLUSION

These findings suggest that insertion of the peritoneal catheter via the Sildenger percutaneous technique is safer with a lower frequency of long-term complications. Rather, it has the advantage of no general anesthesia and a shorter cutaneous incision.

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DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the local ethics committee (Decision number: E-71522473-050.01.04-241662-327).

Informed Consent: All patients included in the study signed informed consent.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All authors contributed to conceptualization and data collection. MI and HD wrote the first draft. All authors contributed to the revision and approval of the last draft.

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Original Article

The Other Side of The Coin in Assisted Peritoneal Dialysis

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ABSTRACT

Background: Assisted peritoneal dialysis (aPD) has long been used worldwide to treat elderly and frail patients with end-stage renal disease. In developed countries, aPD is provided by health professionals, while in developing countries it is provided by family members or caregivers. The main aim of this study was to examine the quality of life (QoL) of caregivers and to investigate its impact on PD.

Methods: We included 31 patients on self-administered peritoneal dialysis and 40 patients on aPD. Patients were compared in terms of peritonitis, hospitalization, and catheter exit site infection. SF-36 questionnaire was administered to family members and caregivers assisting peritoneal dialysis and compared with the control group.

Results: When the SF-36 life scale sections of the assistants were evaluated separately, the median physical function score, median physical role difficulty score, median emotional role difficulty score, median social functioning score, median pain score, mean general health perception and total SF36 score were found to be statistically significantly lower compared to the control group (90 vs 57.5, 100 vs 0, 100 vs 16.7, 100 vs 50, 90 vs 55, 77.4 vs 47, 3020 vs 1575, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p=0.001$, $p<0.001$, $p<0.001$). There was no statistically significant difference between the groups in terms of clinical outcomes such as peritonitis, catheter exit site infection, and the need for hospitalization.

Conclusion: In developing countries, peritoneal dialysis supported by family members can be a convenient, safe, and cost-effective dialysis method. Nevertheless, it can be reasonable to establish measures and policies to enhance the quality of life of caregivers.

Keywords: Assisted peritoneal dialysis, SF-36 quality of life scale, peritonitis, peritoneal dialysis, caregiver

INTRODUCTION

The rate of chronic kidney disease among adults is increasing, leading to a higher incidence of end-stage renal disease (ESRD) requiring renal replacement therapy (1-4) (in my opinion this is better for beginning). Peritoneal dialysis (PD) is the most used type of home dialysis (1). PD requires a specific level of mobility and visual acuity, an intact peritoneum that has not been compromised by surgical intervention, and the ability to acquire and administer demanding daily medical therapy independently. When an individual's ability to engage in self-care is impaired, they may seek the assistance of a caregiver.

In assisted peritoneal dialysis (aPD), caregivers are primarily responsible for carrying out dialysis exchanges. Their daily responsibilities include managing catheter connections and dialysis solutions, configuring and operating the dialysis machine, maintaining records, monitoring the recipient's health, and coordinating care (5).

Some studies have suggested that aPD could increase the utilization of PD among patients (6-8). However, whether aPD attained comparable outcomes to self-care PD remained debatable (9). Moreover, it is crucial to consider the effects of caregiving on PD patients. Given the decreased physical and mental functioning of

assisted patients with PD, it is likely that their caregivers will have a heavy workload.

The SF-36 was developed and validated as a generic short-form instrument for measuring quality of life (QOL) domains. The SF-36 consists of eight QOL domains: PF, physical functioning; RP, physical role; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, emotional role; MH, mental health. Two summary components were constructed to summarize the physical and mental components (PCS and MCS, respectively) (10).

The aim of this study was to examine patients receiving assisted peritoneal dialysis and patients receiving self-administered peritoneal dialysis in terms of outcomes such as peritonitis, frequency of hospitalisation, reasons for hospitalisation and discontinuation of peritoneal dialysis. In addition, to investigate the effect of quality of life of the relatives of patients receiving peritoneal dialysis on these outcomes.

METHODS

Study Design and Participants

This is a multi-center retrospective study. In our study, four different groups of subjects were compared. The first group represented the assisted peritoneal dialysis patients, the second group represented the self-peritoneal dialysis patients, the third group represented the relatives of assisted peritoneal dialysis patients and the fourth group represented the control group consisting of healthy people in the community.

In this study, assisted peritoneal dialysis patients and self-administered peritoneal dialysis patients were compared in terms of frequency of peritonitis, catheter exit site infection, frequency of hospitalisation and reasons for hospitalization. The SF 36 questionnaire was administered to the helpers to determine whether changes in relatives' quality of life had any effect on these outcomes.

Since SF 36 questionnaire results may vary from community to community, SF 36 questionnaire results applied to the relatives were compared with the healthy control group obtained from the same community with similar demographic characteristics.

Height, weight, PD solutions used, number of hospitalizations, episodes of peritonitis, and laboratory findings were extracted from the initial and the last visit of patients who initiated peritoneal dialysis in two centers. The inclusion criteria for the investigation were as follows: (1) having undergone PD for at least three months, (2) being at least 18 years old, (3) not being hospitalized at the time of assessment or within the previous three weeks and (4) having no dementia or psychiatric diagnosis were all recorded from the files.

Family members and caregivers of consenting patients were recruited only if they resided with the patients and met the aforementioned criteria.

The study was approved by the Sakarya University Ethics Committee (approval number 186, 31.05. 2023) and all participants signed informed consent forms.

Questionnaire administered to caregivers.

Demographic information was collected from caregivers and family members, including age, gender, education, ethnicity, occupation, monthly household income, and relationship to the patient.

The quality of life was assessed using Version 1 of the SF-36, and scoring was carried out following the "SF-36 Health Survey Manual and Interpretation Guide" (10).

STATISTICAL ANALYSIS

The uploaded research data was analyzed using IBM SPSS 22 (IBM Statistical Package for the Social Sciences). Numbers and percentages are used to represent categorical variable descriptive statistics. To compare categorical variables using cross tables, the "Pearson Chi-Square Test" and the "Fisher Exact Test" were used. Descriptive statistics for regularly distributed data are provided as mean (±) standard deviation, and for non-normally distributed variables, as median (min-max). The normality distribution of numeric variables was determined using the "Kolmogorov-Smirnov" or "Shapiro-Wilk" tests. The "T for Independent Samples" test was used for normally distributed variables and the "Mann-Whitney U" test was used for non-normally distributed variables when comparing numerical variables between two independent groups. The p value resulting from pairwise comparisons involving three or more subgroups was corrected using the Bonferroni method. P0.05 statistical significance levels were approved.

RESULTS

Demographic characteristics, clinical and laboratory results of the patient group and the group performing aPD are presented in **Table 1**. Patients who had aPD were older ($p<0.001$). There was no statistically significant difference between the groups in terms of gender. When the groups were compared in terms of primary disease, it was found that diabetes mellitus (DM) was more common in the assisted PD group, and chronic glomerulonephritis patients were more common in the unaided PD group ($p=0.045$). Chronic heart failure (CHF) patients were more common in the aPD group ($p=0.023$). It was determined that the continuous ambulatory peritoneal dialysis (CAPD) modality was applied more in the group performing assisted PD ($p=0.016$). Both systolic and diastolic blood pressures (BP) were found to be lower in the aPD group compared to the control group (mean cyst BP 140 mmHg, median diastolic BP 80 mmHg, $p=0.036$, $p=0.001$, respectively).

Table 1. Comparison of demographic and clinical-laboratory results of patients with and without assisted peritoneal dialysis

	Self-care PD, (n=31)	Assisted PD, (n=40)	p- value
Age (years)	50.7±14.5	66.8±12	<0.001[1]
Gender, M/F (%M)	14/17 (45.2%)	19/21 (47.5%)	0.845[2]
Primary Disease, (n) **Diabetes Mellitus** **Hypertension** **Cr.GN** **PKD** **Nephrolithiasis** **Other** **Unknown**	 5 (16.1%) [a] 14 (45.2%) 3 (9.7%) [a] 2 (6.5%) 1 (3.2%) 5 (16.1%) 1 (3.2%)	 17 (42.5%) [b] 12 (30%) 0 (0%) [b] 0 (0%) 2 (5%) 5 (12.5%) 4 (2.8%)	 0.045[2]
CAD (%)	6/25 (19.4%)	16/24 (40%)	0.062[2]
CHF (%)	2/29 (6.5%)	11/29 (27.5%)	0.023[3]
PD Modality, CAPD/APD, (CAPD%)	22/9 (71%)	37/3 (92.5%)	0.016[3]
Extraneal, (%)	17/14 (54.8%)	19/21 (47.5%)	0.540[2]
Follow-up period (month)	33.2 (7-123)	14.2 (5-122)	0.003[3]
Weight (kg)	77.2±18.8	73.1±12.9	0.281[1]
Height (cm)	163 (144-187)	162.5 (146-178)	0.926[3]
SBP mmHg	154±31	140±24	0.036[1]
DBP mmHg	90 (60-130)	80 (60-120)	0.001[3]
Residual urine0 (ml)	1750 (0-4600)	1500 (150-4000)	0.673[3]
Blood urea nitrogen 0 (mg/dL)	55±12	48±18	0.045[1]
Creatinin0 (mg/dL)	5.6 (3.6-14.4)	5.3 (1.2-9.6)	0.149[3]
Uric acid0 (mg/dL)	6.8±1.1	6.1±1.7	0.031[1]
Albumin0(mg/dL)	38±4.1	34±5.3	0.001[1]
Total cholesterol 0(mg/dL)	200±52	180±47	0.080[1]
Triglycerides 0 (mg/dL)	160 (53-545)	111 (37-353)	0.005[3]
Low density lipoprotein 0 (mg/dL)	135±53	110±32	0.022[1]
High density lipoprotein 0 (mg/dL)	43 (29-78)	41 (28-69)	0.830[3]
C reactive protein 0 (mg/dL)	4 (3-36)	10.4 (0.6-106)	0.067[3]
Ferritin 0 (mg/ng)	184 (49-2139)	304 (57-1270)	0.041[3]
Haemoglobin 0 (g/dL)	10.7±1.5	10.8±1.5	0.747[1]
Platelet 0 (c/mL)	231±72	254±86	0.225[1]
C reactive protein/Albumin0	1.1 (0.7-12.5)	3.4 (0.2-29.8)	0.018[3]
Ultrafiltaration0 (ml)	1000 (200-2300)	1150 (0-2500)	0.328[3]
Blood Urea Nitrogen1(mg/dL)	48 (29-89)	42 (21-85)	0.033[3]
Creatinin1 (mg/dL)	6.7 (3.2-15.5)	5.1 (0.93-13.2)	0.003[3]
Uric acid1 (mg/dL)	6.1±1.2	5.7±1.3	0.215[1]
Albumine1	35±4.3	34±4.1	0.242[1]
Total cholesterol 1(mg/dL)	208±53	190±49	0.142[1]
Triglycerides1(mg/dL)	154 (60-473)	126 (47-325)	0.136[3]
Low density lipoprotein1 (mg/dL)	138±38	122±38	0.079[1]
High density lipoprotein1 (mg/dL)	48±11	48±15	0.933[1]
C reactive protein1	8 (3.1-36)	6.9 (0.6-196)	0.614[3]
LDH1 (U/L)	211 (39-439)	170 (22-369)	0.008[3]
Ferritin1	211 (18-1867)	313 (16-1211)	0.028[3]
White Blood Cell1	7.6 (4.5-12.2)	7.1 (4.5-18.4)	0.908[3]
Haemoglobin1	10.7±2.2	10.9±1.8	0.762[1]
Platelet 1	244±76	260±91	0.441[1]
C reactive protein/Albumin1	2.7 (0.8-12.9)	2 (0.2-63)	0.817[3]
Acute Peritonitis, E/H (I%)	2/29 (1.7%)	2/38 (5%)	0.591[4]
Residual urine1 (ml)	1200 (0-3000)	1000 (0-3500)	0.940[3]
Catheter exit site inf. E/H (E%)	4/27 (12.9%)	2/38 (5%)	0.393[4]
PD Program stop, E/H (E%)	8/23 (25.8%)	7/33 (17.5%)	0.395[2]
Hospitalization, E/H (E%)	18/13 (58.1%)	16/24 (40%)	0.131[2]
Reason for admission, (n) (N=34) **Peritonitis** **Anemia** **Catheter dysfunction** **Hypervolemia** **Other infections**	(n=18) 2 (11%) 2 (11.1%) 2 (11.1%) 5 (27.8%) 2 (11.1%)	(n=16) 2 (12.5%) 1 (6.25%) 3 (18.8%) 6 (37.5%) 4 (25%)	 0.439[2]

Cr.GN: chronic glomerulonephritis, PKD: polycystic kidney disease, CAD: coronary artery disease, CHF: congestive heart failure, PD:peritoneal dialysis, CAPD: continuous ambulatory peritoneal dialysis, APD: automated peritoneal dialysis, SBP: systolic blood pressure, DBP: diastolic blood pressure. '0': represents the values when peritoneal dialysis was first started.
'1': represents the values at the last visit.
[1]Independent samples t-test [2]Pearson Chi-Square [3]Man Whitney U test [4]Fisher's Exact Chi-Square

Patients with aPD have lower mean blood ure nitrogen (BUN), mean uric acid, mean albumin, median triglyceride, and mean low density lipoprotein (LDL) (55 vs 48 mg/dl, 6.8 vs 6.1 mg/dl, 38 vs 34 g/L, 160 vs 111 mg, respectively). (LDL, 135 vs 110 mg/dl, p=0.045, p=0.031, p=0.001, p=0.005, p=0.022). On the other

hand, the median ferritin value was higher in the aPD group (184 vs 304, p=0.041). There was no statistically significant difference between the groups in terms of clinical outcomes such as peritonitis, catheter exit site infection, the need for hospitalization, termination of the PD program and the reasons for hospitalization.

Demographic characteristics and SF-36 quality of life scale characteristics of the caregivers and control population are given in **Table 2**. There was no statistically significant difference between the groups in terms of age, gender and educational status. When the SF-36 life scale parts were evaluated separately, the median physical function score, median physical role difficulty score, median emotional role difficulty score, median social functionality score, median pain score, mean general health perception and total SF36 score were found to be statistically significantly lower (respectively). (90 vs 57.5, 100 vs 0, 100 vs 16.7, 100 vs 50, 90 vs 55, 77.4 vs 47, 3020 vs 1575, p<0.001, p<0.001, p<0.001, p<0.001, p=0.001, p <0.001, p<0.001).

DISCUSSION

As aPD is a treatment that requires the aid of a caregiver, it is critical to understand the impact of this modality on patient outcomes as well as the caregiver's quality of life. To our knowledge, this is the first study to examine patient outcomes and life quality of caregivers in aPD.

The demographic and clinical characteristics of the study population's aided and self-care categories were similar. The aPD group was older, had a higher frequency of diabetes and cardiovascular disease, and had more comorbidities than the self-care PD group. Boyer et al. showed that patients who began aPD treatment were twelve years older than those who did not (6). Lobbedez et al. reported in a French study that aPD patients were older and had more comorbidities than self-care patients (11). According to these statistics, the majority of those in need of assistance were elderly, decrepit, physically or mentally handicapped, and afflicted with multiple comorbidities.

Peritonitis rates were comparable in both the assisted and unassisted PD groups. Similarly, Xu et al. reported that patients receiving aided PD experienced similar peritonitis frequency as patients receiving self-carePD (12). Smyth et al. demonstated no link between PD support and survival without peritonitis (13). In a second RDPLF trial, Benabed et al. showed that nurse-assisted PD patients had a lower incidence of peritonitis than self-care PD patients, although family-assisted PD had no protective effect against peritoneal infection (14). Nurse support was related with an increased risk of peritonitis in automated PD patients, according to Verger et al., although supported PD was not associated with an increased risk of peritoneal infection when nurses from the PD center made regular home visits (15). These findings suggested that aided PD had no relationship with peritonitis rates.

In terms of technical issues, catheter malfunction, and transfer to hemodialysis (HD), both groups were comparable. In contrast to our findings, a study of 9822 incident PD patients detected between January 2002 and December 2010 by the RDPLF indicated that assisted patients were less likely to be shifted to HD than self-care patients (16). Querido et al. also discovered that technique survival was greater in PD patients who were assisted than in were self-care PD (17). We believe that by helping some elderly patients who are too weakened to self-dialyze, or patients who need assistance for any medical reason, the risk of PD technical failure can be reduced to a rate comparable to patients who dialyze on their own. Relatively small number and short follow-up

Table 2. Demographics of helpers and their normal controls and characteristics of the SF36 quality of life scale

Items	Control Group, (n=43)	Assistants Group, (n=40)	p
Age(years)	43.3±15.1	46.7±14.7	0.303[1]
Gender, F/M (% female)	23/20 (53.5%)	21/15 (58.3%)	0.666[2]
Education **1. Literate** **2. Primary education** **3. High school**	 3 (7%) 14 (32.6%) 13 (30.2%)	 7 (17.5%) 17 (42.5%) 8 (20%)	0.244[2]
SF36 Quality of Life Scale Features			
Physical function	90 (50-100)	57.5 (0-100)	<0.001[3]
Physical role difficulties	100 (75-100)	0 (0-100)	<0.001[3]
Emotional role difficulties	100 (0-100)	16.7 (0-100)	<0.001[3]
Energy/vitality	56.8±21.7	47±24.2	0.054[1]
Mental health	64.6±18.8	64.6±22.5	0.087[1]
Social functionality	100 (25-100)	50 (0-100)	<0.001[3]
Pain	90 (0-100)	55 (0-100)	0.001[3]
General health perception	77.4±17.5	47±24	<0.001[1]
TotalSF36 score	3020 (2075-3460)	1575 (375-3505)	<0.001[3]

time may cause this discrepancy.

Owing to the high levels of physical disability among aPD patients, caregivers are required to provide assistance with personal care in addition to renal-specific treatment (18). Despite their greater involvement in such practical chores, caregivers of aided PD patients their energy and psychological health scale was comparable to that of the control group. This was similar to prior research, which indicated that caring for PD patients had no negative impact on caregivers' psychology (19). It has also been proposed that this is due to Asian cultural standards and expectations of a cohesive family unit and filial piety (20). The moral responsibility of spouses or children, who made up the vast majority of caregivers in our study, to care for and shelter elderly parents may explain the status of psychological scale. In order to comprehensively investigate the dynamics of reactions across time, it is imperative to conduct replications in diverse situations and employ longitudinal designs.

The scales of the SF-36 test related to physical function, physical role difficulty, emotional role difficulty, social functionality, and pain were significantly lower in the assistants. In the caregiver group, perceptions of general health were lower. This finding is consistent with previous research findings. (21,22) Caregivers of aided PD patients have lower QoL and greater burden than the general population. Because of their heavy workload and elevated burden, caregivers' health suffers, making them more susceptible to depression, anxiety, and other medical issues. Consequently, public and private health expenditure has increased (23). It also affects the care provided to patients, and consequently, the efficacy of their treatment (23). Therapies that enhance well-being are required to alleviate these severe conditions (24-26).

Therapies with multiple components that address both disease-related difficulties and personal requirements of caregivers are more likely to yield substantial benefits. In addition, because it will prevent chronic kidney disease complications in patients and health problems in caregivers, it is anticipated that it will not only impact the caregiver-patient relationship but also reduce public and private health expenditures (23).

Information and communication technology-based (ICT)-based interventions are promising. Information and communication technologies are instruments that can be used to unite individuals for common purposes. According to a 2014 systematic review, telehealth enhances the well-being of family caregivers of patients with dementia, cancer, stroke, heart disease, spinal cord injury, brain injury, mental illness, and chronic diseases in general. The technological resources used were video conferencing, text messaging, phone calls, and web-based data. The findings revealed improvements in mental and physical health, quality of life, caregiver knowledge and skills, social support, and coping abilities (27). ICT has been identified as a viable option for future research because the QoL of caregivers of patients with PD is comparable to that of caregivers of patients with other chronic conditions (27,28). Another option is to provide a professional support to PD patients. Several nations have developed aPD strategies over the past few decades. The model varies based on the type of assistant employed and level of assistance offered. With positive clinical outcomes, both health care and non-health care assistants have been utilized (29). To address the difficulties faced by caregivers, mechanisms involving specialists should be developed.

The study's limitations arise from its relatively small sample size and cross-sectional design.

CONCLUSION

The results of this study imply that caregiver burden and quality of life concerns should not preclude the use of aPD, thereby extending the efficacy of assisted PD for survival and peritonitis outcomes established in earlier studies (15,30). Assisted PD may make PD a viable treatment option for more patients, including those who cannot care for themselves or lack confidence in self-administration, without negatively influencing the patient or caregiver (31). This is especially essential in light of the increasing number of ESRD patients and the need to relocate dialysis care away from overcrowded HD facilities to reduce healthcare expenditures (32). To address the difficulties faced by caregivers, mechanisms involving specialists may be developed. The use of information and communication technology (ICT) is the second potential strategy to overcome the difficulties of caregivers.

DECLARATIONS

Author contributions: Z.E.: Principal investigator, conceptualization, methodology, investigation, writing—original draft preparation, Y.A.: Editing, supervision, project administration

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Sakarya University Ethics Committee(approval number 186, 31.05. 2023)

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study, and they were allowed to withdraw at any time.

Data Availability Statement: All data reported in the article are available in anonymized form upon request.

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Original Article

The Relationship Between the HALP Score and Gastric Cancer Prognosis

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ABSTRACT

Background: Gastric adenocarcinoma is the fifth most common malignancy worldwide and the third leading cause of cancer-related deaths. As most patients are diagnosed in the advanced stage of the disease, the prognosis is dismal. Therefore, researchers have developed various scoring systems to predict prognostic factors. One of these is the HALP scale, which consists of hemoglobin, albumin, lymphocytes and platelets. This study aims to assess the utility of the HALP score as a prognostic tool in predicting the clinical outcomes of patients with gastric adenocarcinoma.

Methods: A retrospective review of patients who underwent gastrectomy for gastric cancer between 2018 and 2021 in the Department of Surgical Oncology, Gulhane Medical School Training and Research Hospital, University of Health Sciences. A total of 158 patients who underwent surgery for the diagnosis of gastric adenocarcinoma were included in the study. Hemoglobin, albumin, lymphocytes and platelet values were obtained from patient files. HALP scores were calculated and correlations with clinicopathologic factors were investigated.

Results: We found a significant negative correlation between the HALP score and T stage and N stage. Increasing the HALP score increases the likelihood of early-stage disease ($p= 0.008$ and $p= 0.001$). We found a significant negative correlation between the HALP score and the number of metastatic lymph nodes and tumor diameter ($p<0.001$ and $p<0.001$). One unit increase in HALP score leads to a 4.7 unit decrease in tumor diameter and a 14.8 unit decrease in metastatic lymph node count.

Conclusion: This study provides insights into the potential utility of the HALP score in predicting clinical outcomes for gastric cancer patients. While these findings are promising, research with large patient data is essential to validate the prognostic value of the HALP score and determine its clinical applicability. The HALP score may assist clinicians in risk stratification and therapeutic decision-making, and ultimately contributing to improved patient outcomes in the management of gastric cancer.

Keywords: Gastric cancer, HALP score, mortality, prognosis

INTRODUCTION

Gastric adenocarcinoma is the fifth most common malignancy worldwide and the third leading cause of cancer-related deaths (1). Adenocarcinomas comprise more than 95% of all gastric cancer cases histopathologically (2).

As most patients are diagnosed in the advanced stage of the disease, the prognosis is dismal (3). In the context of gastric adenocarcinoma, prognostic factors are currently limited to clinicopathological properties, such as tumor size, grade, invasion, lymph node involvement, and molecular markers like HER2 overexpression (4). Nevertheless, there may be significant differences in survival rates between patients with the same TNM stage. These variations have led scientists to search for new biomarkers to accurately predict the prognosis.

One such biomarker is the hemoglobin, albumin, lymphocyte, and platelet (HALP) score calculated using HALP scoring. A review of the literature reveals that the first article on gastric cancer and the development

of HALP as a prognostic tool was published in 2015 by Chen et al (5). The HALP score, evaluating both the immune system and nutritional condition, is valuable as a prognostic factor in many cancer types, particularly gastrointestinal malignancies (6).

The aim of this study is to assess the utility of the HALP score as a prognostic tool in predicting the clinical outcomes of patients with gastric adenocarcinoma and to identify subgroups with a significant risk of poor survival.

METHODS

Study Population

A retrospective review of patients who underwent gastrectomy for gastric cancer between 2018 and 2021 in the Department of Surgical Oncology, Gulhane Medical School Training and Research Hospital, University of Health Sciences. A total of 166 patients were identified. Five patients with pathology results showing complete response after neoadjuvant treatment and three patients with pathology diagnosis of non-adeno cancer (neuroendocrine tumor, lymphoma) were excluded from the study. A total of 158 patients who underwent surgery for the diagnosis of gastric adenocarcinoma were included in the study. There was no upper age limit in our study and all individuals over 18 years of age were included.

Establishment of HALP Score

Preoperative blood samples obtained during the preparation for anesthesia were analyzed for Hgb, albumin, lymphocytes, and platelets. The Hemogram, Albumin, Lymphocyte, and Platelet (HALP) score for each patient was retrospectively calculated using the following formula:

HALP Score = (Hemoglobin level (g/dL) × Lymphocyte count (10^3/μL)) x (Albumin level (g/dL) / Platelet count (10^3/μL))

Study Design

We retrospectively reviewed the patient files. Clinicopathologic parameters and demographic data were extracted. First, the HALP scores of the patients were calculated by the formula. The relationship between the HALP score and demographic and clinicopathologic parameters was evaluated. The possible relationship between HALP score and T stage, N stage, number of lymph node metastases, tumor size, lymphovascular invasion (LVI), and perineural invasion (PNI), which have a significant role in the prognosis of gastric cancer, was investigated. A regression analysis was performed to determine the efficacy level of these parameters that have a statistically significant relationship with the HALP score. The impact of the HALP score on early gastric cancer prognosis was investigated. Survival data of the patients were recorded.

STATISTICAL ANALYSIS

Data were analyzed by using SPSS version 22.00. For the homogeneity and normality analysis of the scaled data, Kolmogorov-Smirnov and Shapiro-Wilks tests were performed. One-Way ANOVA, Kruskal Wallis, post hoc multiple comparison (Bonferroni) tests were utilized for the analysis of multiple groups. The Mann Whitney-U test was used in the two-group scaled analysis. Univariate regression was calculated by Binary Logistic regression and Multinominal Logistic regression analysis model. The Spearman correlation test was performed for dependency analysis of the scaled data. $P<0.05$ was deemed statistically significant.

RESULTS

Patient Characteristics

The 158 patients who underwent gastrectomy for gastric adenocarcinoma were evaluated in this study. 101 of the patients were male and 57 were female. The mean age was 61.70 years (range 27-88). The tumor was localized in the small curvature in 50 patients, the antrum in 59 patients, and the proximal in 49 patients. In 52.5% of the patients, gastrectomy was performed following neoadjuvant treatment. None of our patients had peritoneal carcinomatosis or intra-abdominal ascites. 62 (39.2%) and 63 (39.9%) patients were in the T4 and T3 stages, respectively. There were 111 patients with lymph node metastasis, and the mean count of metastatic lymph nodes was 7.02. 120 patients had LVI and 105 patients had PNI. The mean value of hemoglobin (Hgb) was 11.86 g/dL (range 7.5-16.1), the mean value of albumin was 3.51 g/dL (range 2.10-4.60), the mean value of lymphocyte was 1.73 10^3 /μl (range 0.3-4) and the mean value of the platelet was 252.27 10^3 /μl (range 75-531). The median value of the HALP score was 0.32 (range 0.05-1.14). Of the patients, 87 were alive, and follow-up was ongoing. The demographic and clinicopathologic distribution of all patients is detailed in **Table 1**.

Comparison of the HALP Score with Clinicopathological factors

First, we performed normality and homogeneity tests on the HALP score. We found that they were not equally distributed in both analyses. There was no significant difference in the distribution of the median value of the HALP score by gender, showing a homogeneous distribution ($p=0.947$). There was no significant difference in the distribution of the HALP score according to tumor localization and it was the highest in patients with the antrum localization. A significant difference was found in the distribution of the HALP score by T stage ($p=0.008$). This difference is attributed to the relationship between the median HALP score of T1 and T4 patients (Post-Hoc Bonferroni test T1 between T4 HALP score $p=0.024$). Similarly, there was a significant difference in the distribution of the HALP scores of

Table 1. Demographic characteristics of patients

Age, years, mean±SD, range	**61.70±12.21 (27-88)**
Gender, n(%)	
Male	**101 (%63.9)**
Female	**57 (%36.1)**
Tumor Localization, n(%)	
Lesser curvature	**50 (%31.6)**
Distal	**59 (%37.3)**
Proximal	**49 (%31)**
Operation, n(%)	
Distal Gastrectomy	**54 (%34.2)**
Total Gastrectomy	**104 (%65.8)**
Neoadjuvant Treatment, n(%)	
No	**83 (%52.5)**
Yes	**75 (%47.5)**
Tumor size, mm, mean±SD, range	**4.99±3.15 (1-16)**
Degree of T invasion, n(%)	
T1	**21 (%13.3)**
T2	**12 (%7.6)**
T3	**63 (%39.9)**
T4	**62 (%39.2)**
Lymph Node Dissection, number, mean±SD, range	**27.70±12.42 (13-66)**
Lymph Node Metastasis, number, mean±SD, range	**7.02±9.03 (0-43)**
N stage grade, n(%)	
N0	**47 (%29.7)**
N1	**31 (%19.6)**
N2	**28 (%17.7)**
N3	**52 (%32.9)**
TNM Stage, n(%)	
Stage 1	**24 (%15.2)**
Stage 2	**32 (%20.3)**
Stage 3	**92 (%58.2)**
Stage 4	**10 (%6.3)**
LVİ, n(%)	
No	**38 (%24.1)**
Yes	**120 (%75.9)**
PNİ, n(%)	
No	**53 (%33.5)**
Yes	**105 (%66.5)**
Hgb, g/dL, mean±SD, range	**11.86±1.84 (7.50-16.10)**
Albumine, g/dL, mean±SD, range	**3.51±0.46 (2.10-4.60)**
Lymphocyte, 10^3 /µl, mean±SD, range	**1.73±0.69 (0.30-4)**
Platelet, 10^3 /µl, mean±SD, range	**252.27±85.53 (75-531)**
HALP Score, mean±SD, range	**0.32±0.19 (0.05-1.14)**
Survival, n(%)	
Li Table 1. Demographic Characteristics of Patients ve Ex	**87 (%55.1)**
	71 (%44.9)

SS; standard deviation, LVİ; lympho-vascular invasion, PNİ; peri-neural invasion, Hgb; Hemoglobin

the N stages (p=0.001). This difference is attributed to the relationship between the median HALP score of the n0 group (0.37) and the n3 group (0.21) (Post-Hoc Bonferroni test n0 between n3 HALP score p=0.001). We observed a significant distribution of LVI and PNI levels in the HALP scores (p=0.013 and p=0.009). The median HALP score was 0.36 in LVI-negative patients and 0.29 in LVI-positive patients. Similarly, the median HALP score of PNI-negative patients was 0.36 and the median HALP score of PNI-positive patients was 0.27 (Table 2).

We investigated the correlation between the HALP score and the number of metastatic lymph nodes and tumor diameter. We determined a significant negative correlation between both parameters and the HALP score (Table 3). Each one-unit increase in the HALP score leads to a 14.8240 unit decrease in the number of metastatic lymph nodes (p<0.001). Similarly, a one-unit increase in the HALP score leads to a 4.775 unit decrease in tumor diameter (p<0.001).

Univariate analysis of the HALP score for T stage, N stage, LVI status and PNI status

We performed a regression analysis to evaluate the effect of the HALP score on T stage, N stage, LVI, and PNI levels. We previously found that the HALP score was lower in T4 group patients and higher in T1 group patients. In the multinominal logistic regression, considering T4 patients as the reference category, the probability of higher HALP scores in T1 and T2 group patients was statistically significant. This probability was higher in T1 patients and was increased by 3.806 times. There was no significant relationship between T3 and T4 group patients. We accepted n3 patients as the reference category in the N stage analysis. The probability of having high HALP scores in the patients in the n0 and n2 groups was statistically significant compared to the patients in the n3 group. Binary logistic regression analysis was performed for LVI and PNI. We found a negative correlation with the HALP score in both parameters. An increase in the HALP score was associated with an increased likelihood of negative LVI and PNI (OR=0.133, 95% CI: 0.017-0.733, p=0.022 and OR=0.129, 95% CI: 0.022-0.759, p=0.024) (Table 4).

DISCUSSION

A standardized neoadjuvant/adjuvant chemotherapy and surgical treatment protocol is implemented for gastric cancer with well-defined guidelines. The effectiveness of this treatment is evaluated by analyzing the results of surgical treatment and survival analysis based on clinical and pathological stage. However, the standardized treatment approaches for tumor size, lymph status, metastasis status and disease survival analyses have shortcomings such as the inability to evaluate individual patient factors. The HALP score, calculated using hemoglobin, albumin, lymphocyte and platelet parameters, is used as an indicator of both the immunological and nutritional status of patients. In the last several years, HALP score has emerged in the literature as a new prognostic biomarker that has been used to predict a number of clinical outcomes in the context of various neoplasms. XU et al published a negative correlation between HALP score and prognosis

Table 2. Distribution of Clinico-pathologic factors according to HALP scoring system

Clinico-pathological Factors	HALP Score, median, range	P değeri
Gender, n(%)		
Male	0.30 (0.052-0.898)	p=0.947[U]
Female	0.29 (0.057-1.143)	
Tumor Localization, n(%)		
Lesser Curvature	0.28 (0.063-0.985)	
Antrum	0.34 (0.057-0.898)	p=0.160[H]
Kardia	0.29 (0.052-1.143)	
Degree of T invasion, n(%)		
T1	0.41 (0.11-0.898)	
T2	0.36 (0.057-0.702)	p=0.008[H]
T3	0.33 (0.052-0.985)	
T4	0.24 (0.057-1.143)	
Degree of N invasion, n(%)		
N0	0.37 (0.086-0.898)	
N1	0.34 (0.052-0.985)	p=0.001[H]
N2	0.32 (0.083-1.143)	
N3	0.21 (0.057-0.707)	
TNM Stage, n(%)		
Stage 1	0.42 (0.110-0.898)	
Stage 2	0.29 (0.057-0.766)	p<0.001[H]
Stage 3	0.29 (0.052-1.143)	
Stage 4	0,13 (0,068-0,411)	
LVİ, n(%)		
No	0.36 (0.069-0.766)	p=0.013[U]
Yes	0.29 (0.052-1.143)	

in rectal cancer patients. Sun e al, showed that low HALP was associated with worse overall survival, outperforming other hematological markers in biliary tract adenocancer patients (7,8).

In this study, we evaluated the effectiveness of the HALP score in a large series of gastric adenocarcinoma patients. As remarkable results of our study, the number of metastatic lymph nodes and tumor diameter determined a significant negative correlation with the HALP score (p<0.001). An increase in the HALP score was associated with an increased likelihood of negative lymphovascular invasion and perineural invasion (OR=0.133, 95% CI: 0.017-0.733, p=0.022 and OR=0.129, 95% CI: 0.022-0.759, p=0.024).

The HALP score, calculated using hemoglobin, albumin, lymphocyte and platelet parameters, is used as an indicator of both the immunological and nutritional status of patients. Anemia is a common paraneoplastic syndrome in patients with malignancies, especially in esophageal and gastric cancers located in the upper digestive tract, due to both oral intake disorders and chronic bleeding from the tumor (9). What is the role of these HALP score components in cancer pathogenesis and the mechanisms that are hypothesized to underlie them?

Platelets are known to secrete vascular endothelial growth factor (VEGF) and aggravate tumor angiogenesis. For this reason, they are thought to play a key role in the metastasis of tumor cells (10,11). Chronic low hemoglobin is a well-documented, cheap and easily accessible parameter that occurs in cancer patients by various mechanisms. One of the roles of chronic low hemoglobin in cancer patients is the secretion of

Table 3. Distribution of Clinico-pathologic factors according to HALP scoring system

Correlation of Number of lymph node dissection number					
Clinicopathological Factors		N		rho	p value
1- Age		158		-0.190	0.017
2- Tumor Diameter		158		-0.370	<0.001
3- Lymph Node Metastasis		158		-0.346	<0.001
Regression					
Dependent Variables	Independent Variable	B	95% Cl for B	t	p value
1- Age	HALP Score	-11.926	-21.877-1.975	-2.367	0.019
2- Tumor Diameter		-4.775	-7.276-2.274	-3.771	<0.001
3- Lymph Node Metastasis		-14.824	-21.935-7.714	-4.118	<0.001

Table 4. Univariate analysis of HALP score for T stage, N stage, LVİ status and PNİ status of Clinico-pathologic factors according to HALP scoring system

Variables	B	O.R	95% Cl for O.R		P value
			Lower	Upper	
T Stage					
T1	3.806	44.966	3.205	630.806	0.005
T2	3i540	34.473	1.494	795.601	0.027
T3	1.632	5.112	0.625	41.820	0.128
Reference category T4					
N Stage					
n0	4.708	110.83	8.531	1439.91	<0.001
n1	2.772	15.99	0.964	265.34	0.053
n2	3.660	38.88	2.303	656.32	0.001
Reference category n3					
LVİ	-2.184	0.113	0.017	0.733	0.022
PNİ	-2.046	0.129	0.022	0.759	0.024

proinflammatory cytokines such as interleukin-6 (IL-6) from immune cells. IL-6, together with IL- and TNF alpha, is one of the most potent proinflammatory cytokines known. IL-6 stimulates Hepcidin release from the liver and inhibits iron absorption and release by cancer cells (12-14). Another feature is that it reduces erythropoiesis (15).

Two significant parameters affecting blood albumin levels are nutritional status and metabolic status of the patient. CRP and albumin concentrations, utilized in various prognostic scoring systems, were used in many studies involving patients with malignancies and evaluating survival and treatment efficacy (16-18). In one of these studies, Liv et al. showed a decrease in mortality rates in cachectic malignancy patients whose serum albumin levels were increased. As a result of these studies, albumin has been accepted as a good marker for prognosis (19). In cancer patients, lymphocytes are thought to play an important role in the detection and elimination of tumor cells. Based on this idea, lymphopenia is thought to play an important role in prognosis (20).

In order to have an idea about the prognosis of patients with malignancies, the HALP score includes all four of these parameters. Platelets are included in the denominator of the calculation, while hemogram, albumin and lymphocytes are in the numerator. Therefore, a high HALP score is used as a positive indicator of prognosis to identify patients with low immune-nutritional function and to determine risk stratification.

The present study on gastric adenocarcinoma shows that the evaluation of HALP score as a prognostic index is useful considering the publications on other cancer types in the literature. The main discussion at this point is whether the results of the HALP score should be perceived as a prognostic index or evaluated as a precautionary measure for possible clinical outcomes (21). There are limitations regarding the practical use of this score, the timing of calculation and its contribution to treatment planning. The clinical reflection of this prognostic index will be meaningful if inferences can be derived on how to plan the treatment of patients with significant cutoff values obtained from retrospective cases. Clarification of the clinical implications at this stage, such as whether a nutritional or immunomodulatory supportive treatment is to be implemented based on the HALP score, or whether treatment should be prolonged, changed or discontinued early in the planning of possible neoadjuvant treatment, would be the potential subject of prospective randomized studies.

Among patients with resectable disease, including stage III/IV patients, nomograms based on T stage and N stage, comprehensive treatment, age at diagnosis, grade and tumor size perform well in personalized prediction of likely survival (22). The HALP score provides a chance to intervene in possible preoperative treatment or nutritional status, which may add dynamism and clinical relevance to the HALP score.

In conclusion, our study provides a framework for investigating the prognostic potential of the HALP score in gastric cancer. Real-world research efforts are required to confirm its clinical utility and to pave the way for improved patient outcomes in the management of this challenging malignancy.

DECLARATIONS

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Original Article

Investigation of Obesity Prevalence in Adolescent Children in Şanlıurfa Province and Its Relationship with Parental Obesity

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ABSTRACT

Background: Adolescent children obesity is a global public health concern, with increasing prevalence worldwide. This study aims to investigate the prevalence of adolescent children obesity in Şanlıurfa, Turkey, a region characterized by high fertility rates and relatively low socio-economic status, and to explore the demographic and lifestyle factors associated with childhood obesity.

Methods: 176 adolescent children aged 10-17 were evaluated. Data on demographics, family income, residential location, parental professions, the presence of siblings with obesity, fast food consumption, and social media usage were collected. Body Mass Index (BMI) was calculated, and children were categorized into groups based on weight status. Various statistical methods, including chi-square tests, t-tests, analysis of variance, logistic regression, and correlation analysis, were employed to analyze the data.

Results: The study found a combined prevalence of obesity and overweight in adolescent children of 22.7%. Obesity prevalence among children aged 10-17 years was found 8.5%. Children with obesity or overweight were older, had more siblings, had a greater incidence of obesity among siblings, and had a higher frequency of fast food consumption compared to their counterparts ($p<0.05$). Maternal BMI was significantly associated with adolescent children's obesity ($p<0.05$). Low family income was a notable factor in adolescent children with obesity or overweight ($p=0.019$). However, there was no statistically significant difference in obesity rates between rural and urban areas ($p=0.068$).

Conclusion: This study highlights the prevalence of adolescent obesity among children in Şanlıurfa, Turkey. Although it is relatively lower than in some other low-income regions, it aligns with global trends.

Keywords: Adolescent, obesity, Şanlıurfa, prevalence

INTRODUCTION

Obesity among adolescent children, particularly in low-income regions, has become a growing concern in public health. The World Health Organization (WHO) defines overweight and obesity as conditions characterized by abnormal or excessive fat accumulation that pose a significant risk to health (1). For older children and adolescents, different growth references are utilized. The WHO 2007 Growth Reference, for instance, is recommended for those aged 5–19 years. In this reference, overweight is defined as a BMI greater than or equal to 1 standard deviation (SD) above the median for age and sex, while obesity is defined as a BMI greater than or equal to 2 SD above the median for age and sex. The WHO 2006 Growth Standard is recommended in many countries for children aged 0–5 years, and in the United States for children aged 0–2 years (2).

Between 1975 and 2016, there was a substantial increase in the global age-standardized prevalence of obesity among children and adolescents aged 5–19 years. Specifically, for girls, this prevalence rose from 0.7% to 5.6%, while for boys, it increased from 0.9% to 7.8%. The reflections of this rapid obesity rate change in the world have also been seen in this age group in Turkey. Salman et. al reported a higher prevalence of obesity among Turkish children during the COVID-19 pandemic. In their report, the prevalence raised up to

13.6 among children over 11 years old by 2022 (3).

Previous studies from Turkey revealed a broad variation range according to cities in Turkey (4). This variation rises on variations of the socioeconomic status of the regions.

Şanlıurfa is one of the most crowded cities in Turkey and has the highest fertility rate (3.59%) (5). The child population constitutes a very significant part of the total population (~40%) (6). However, the obesity rate among Children in Şanlıurfa is unclear.

This study aims to estimate obesity among adolescent children in Şanlıurfa aged 10-17 years.

METHODS

The data of children aged 10-17 years who applied as outpatients to Şanlıurfa Training and Research Hospital Pediatric Polyclinic were examined. Children with recent illnesses that caused weight change (diarrhea, long-term infection, those who underwent surgery, children with trauma, etc.) were excluded. Data were collected from the hospital software.

The demographic characteristics of the children and their parents were noted. BMIs were calculated according to CDC reference percentile ranges and children were classified as underweight (BMI ≤5), normal weight (BMI between 5-85), overweight (BMI between 85-95), and obese (BMI ≥95) (6).

For epidemiological and clinical purposes, simple anthropometric measures are commonly employed as screening tools to assess overweight and obesity in this age group. One of the primary metrics used is Body Mass Index (BMI), calculated as weight divided by height squared (kg/m^2). BMI serves as an indirect measure of body fatness and is compared to population growth references adjusted for sex and age (7,8). Children's eating habits also were analyzed.

Statistical Analysis

Data analysis was performed using a statistical package program (SPSS for Windows version 17.0, IBM Corp., Armonk, NY, USA). The distribution of continuous variables was tested using the Kolmogorov-Smirnov test. Descriptive parameters were presented as mean ± standard deviation for parametric variables. Categorical variables were compared using the Chi-Square test. Paired-samples t-test was used to compare variables between the two groups. Parametric Pearson's correlation analysis was performed to demonstrate the correlation between variables. Two-tailed p-values <0.05 were considered statistically significant with a 95% confidence interval.

RESULTS

A total of 176 adolescent children between the ages of 10 and 17 were evaluated. The study found that 51.7% of the participants were girls, while 48.3% were boys. Among these children, 15 were classified as obese, which accounts for 8.5% of the total participants, and 25 were categorized as overweight, representing 14.2% of the sample. The combined prevalence of obese and overweight adolescent children was 22.7%, a statistically significant result (p <0.001). Furthermore, it was observed that 9 of the obese adolescent children were girls, while 6 were boys. On average, each family had a mean child count of 4.09±1.88.

The study examined the demographic characteristics of children's families based on the presence of obesity and overweight (Table 1). To facilitate the analysis, obese and overweight adolescent children were grouped together as Group 1, while the remaining participants were categorized as Group 2 (Table 2). Group 1 was found to have several distinguishing features, including older age (14.25±2.68 years in Group 1 vs. 11.06±2.02 years in Group 2), a higher number of siblings (4.89±1.46 vs. 3.92±1.76), a greater incidence of obesity among siblings (p = 0.015), and a higher frequency of fast food consumption more than once a week (29 in Group 1 vs. 42 in Group 2, p = 0.027). Additionally, the study explored the BMI of children and their parents. Children in Group 1 had a significantly higher BMI compared to those in Group 2 (p <0.001). Mothers of children in Group 1 also had higher BMIs (p= 0.042), while fathers' BMIs did not significantly differ between the two groups (p= 0.215).

Table 1. Demographic features

Gender, boys/girls, n, %	85(41.3%)/ 91(51.7%)
Age, years	12.59±1.90
Weight status, n, %	
• **Underweight**	12 (6.8%)
• **Normal weight**	124 (70.4%)
• **Overweight**	25 (14.2%)
• **Obese**	15 (8.5%)
***Family income;**	
• **Low**	73 (41.5%)
• **Moderate**	101 (57.4%)
• **High**	2 (1.1)

*: Total income was calculated for each family according to children count and total salary.

Income levels were another factor considered in the analysis. Children in Group 1 were likelier to come from families with low incomes (p = 0.019), while children in Group 2 had moderate to high family incomes.

The study also examined residential locations and found a trend towards higher obesity rates in rural areas, although this difference was not statistically significant

Table 2. Comparison of the two groups

	Group 1 (Obese + Overweight), n=40	Group 2 (Except Group 1), n=136	P value
Age, years	14.25±2.68	11.06±2.02	**0.025**
Gender, male/female, n	17/23	68/68	0.210
BMI, kg/m^2 • Child • Mother • Father	 26.87±3.89 28.68±5.37 26.34±4.53	 19.25±4.87 26.45±3.75 25.56±3.46	 **<0.001** **<0.042** 0.215
Children count, n	4.89±1.46	3.92±1.76	**0.030**
Income, yes • Low • Moderate + High	 13 27	 60 76	 **0.019**
Residential, n • Rural • Urban	 13 27	 68 68	 0.068
Profession, yes/no, n Mother Father	 10/30 38/2	 6/130 131/5	 **0.002** 0.925
Siblings with obesity, yes/no, n	8/32	5/131	**0.015**
fast food eating habit more than once a week, yes/no, n	 29/11	 42/94	 **0.027**
*Social media use habits, n • ≥ 2 hours/day • < 2 hours/day	 25 15	 22 124	 **0.035**

(p= 0.068). The profession of parents (mothers: p= 0.002, fathers: p= 0.925), the presence of siblings with obesity, and social media usage habits (more than 2 hours per day: p= 0.035) were all associated with Group 1 (obese and overweight children).

Table 2 provides an overview of the demographic characteristics of children's families categorized by the presence of obesity and overweight. Given the relatively low number of obese children, we opted to combine both obese and overweight children into a single group, referred to as Group 1, while the remaining participants were grouped under Group 2. Group 1 was older, had more siblings, and more obese siblings.

DISCUSSION

Previous research from Turkey has demonstrated a wide variation in obesity prevalence across different cities, strongly linked to socioeconomic disparities. Şanlıurfa, with its high fertility rate and a significant proportion of children in the population, presents a unique setting to study childhood obesity, yet data on obesity rates in this region remain scarce. Due to the small sample size and the localized nature of the study, it would not be appropriate to generalize these results to the entire Şanlıurfa province. However, it can be noted that this represents the prevalence only among adolescents who presented to the hospital. This study demonstrated that childhood obesity has a prevalence of 8.5% in adolescent children living in Şanlıurfa and demonstrates a lower prevalence compared to children living in other regions of Turkey.

The prevalence of childhood overweight and obesity is on the rise in numerous countries, affecting children across all age groups, from preschoolers under the age of 5 to school-aged children and adolescents between 10 and 19 years. Beyond the immediate health concerns it poses for children, childhood obesity also elevates the risk of obesity and noncommunicable diseases persisting into adulthood. This underlines the far-reaching consequences and challenges posed by this public health problem (9). Overweight and obesity in childhood is an increasing problem for the low and middleincome countries of the World (10).

The prevalence of child obesity in Turkey is increasing in line with the trends in Europe and the World (3,11). Şanlıurfa attracts attention as the most fertile city in Turkey with an average of 3.89 children per family, and according to statistics, this city is seen as a low-income and low sociocultural region. For this reason, the child population is quite dense and data on child obesity becomes important for public health planning. In our specific region of Şanlıurfa, Salman et al. reported an alarming increase in obesity prevalence among Turkish children during the COVID-19 pandemic, reaching 13.6% among children over 11 years by 2022 (12). These findings underline the urgency of addressing childhood

obesity as a pressing public health issue, particularly in low-income regions.

Our findings revealed a combined prevalence of obese and overweight adolescent children at 22.7%, a statistically significant result ($p < 0.001$). This prevalence aligns with the global trend of increasing childhood obesity rates and highlights the need for targeted interventions in Şanlıurfa to address this issue. However, obesity prevalence was relatively found low compared to other low income regions in Turkey and in the World (11,13). This is an interesting part of the study. Children in the obese or overweight group (Group 1) were older, had a higher number of siblings, a greater incidence of obesity among siblings, and a higher frequency of fast food consumption more than once a week compared to their counterparts in Group 2. These findings are consistent with existing literature on the multifaceted nature of childhood obesity and its associations with dietary habits and familial factors (12,14)

Our study also explored the BMI of children and their parents. Mothers of children in Group 1 also had higher BMIs similar to previous studies, underscoring the potential influence of familial genetics and lifestyle on childhood obesity. These results emphasize the importance of involving families in obesity prevention and management efforts (12-15). Childhood obesity is substantially associated with maternal obesity rather than father obesity, as well as in our cohort (15).

Income levels emerged as a significant factor in our analysis, with children in Group 1 more likely to come from low-income families. These findings align with previous research that highlights the impact of socioeconomic status on childhood obesity (10-14).

In summary, this clinical research study highlighted significant differences in demographics and lifestyle factors between children with obesity or overweight (Group 1) and those without (Group 2). These findings provide valuable insights into the potential risk factors and characteristics associated with childhood obesity in the studied population.

In conclusion, our study provides valuable insights into the prevalence and factors associated with childhood obesity in Şanlıurfa, shedding light on a region with limited existing data on this issue. The findings underscore the urgent need for tailored public health interventions that address the multifaceted nature of childhood obesity, including dietary habits, familial influences, and socioeconomic disparities. Further research is warranted to understand the long-term consequences of childhood obesity in this specific context and to evaluate the effectiveness of targeted intervention strategies.

Limitations of The Study

The study sample consisted of 176 adolescent children in a specific region of Turkey. While the findings provide localized insights, the relatively small sample size and the focus on a single region may limit the generalizability of the results to the broader population.The study employed a cross-sectional design, which captures data at a single point in time. This design limits the ability to establish causation or track changes in obesity prevalence over time. Longitudinal studies would provide a more comprehensive understanding of childhood obesity trends. The data relied on parental reports, particularly concerning lifestyle factors such as dietary habits and social media usage. This introduces the potential for recall bias, as responses may not accurately reflect actual behavior. Additionally, self-reported income levels may not always align with the actual financial situation. The study's exclusive focus on Şanlıurfa, a region known for specific cultural and demographic characteristics, may not fully capture the diversity of the Turkish population. Variations in dietary habits, lifestyle, and socioeconomic factors may not be represented. The study did not explore the potential impact of external factors, such as government policies, healthcare infrastructure, or regional initiatives aimed at childhood obesity prevention. These factors could significantly influence the prevalence and characteristics of childhood obesity in the region. While the study observed associations between maternal BMI and childhood obesity, paternal BMI did not show significant differences between the groups. This discrepancy requires further investigation to better understand the role of parental obesity in childhood obesity within this context. The study did not account for temporal factors, such as seasonal variations or changes in lifestyle and dietary habits over time, which can influence childhood obesity prevalence. The study relied on self-reporting for certain variables, such as social media usage and dietary habits. This approach may be susceptible to social desirability bias, where participants provide responses they believe are socially acceptable. The study did not collect data on the physical activity levels of adolescent children, which is a crucial component in understanding and addressing childhood obesity.

ETHICAL DECLARATIONS

Conflict of Interest Statement: The author declares no conflicts of interest related to this research.

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Ethical Approval: The study protocol was approved by the Harran University Clinical Research Ethics Board (Project Number: HRU/23.18.20), and written informed consent was obtained from all participants before they participated in the study. This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subjects.

Informed Consent: The mothers were first informed about the study and then signed written consent forms.

Author Contributions: The authors declared that they all participated in the design, execution, and analysis of the study and that they approved the final version of the paper.

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Case Report

Bilateral Subcapsular Cataract in A Patient with Crohn's Disease Taking Oral Budesonide Therapy: A Case Report

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ABSTRACT
Crohn's disease is a chronic, inflammatory disease of the gastrointestinal tract, which can progress with remission and flares. In order to maintain remission, initially; systemic glucocorticoids such as prednisolone are used. However, since these traditional glucocorticoids have too many side effects, second-generation drugs such as budesonide, which has much fewer systemic side effects, are now used. However, in the case we presented, a bilateral posterior subcapsular cataract developed in a Crohn's patient followed up with oral budesonide therapy. It was seen that there was no such case report in the literature.

Keywords: Budesonide, Crohn's disease, cataract

INTRODUCTION
Crohn's disease (CD) is a chronic, progressive, inflammatory disease involving any localization of the gastrointestinal tract. CD progresses with remissions and attacks. There are periods of remission and attacks in the natural course of this disease, so the aim of treatment is to achieve remission and then maintain it. Systemic glucocorticosteroids (GCs), such as prednisone, prednisolone, or cortisone, are an effective treatment for CD; however, they are associated with clinically important adverse events, such as suppression of the pituitary–adrenal axis, impaired glucose tolerance, cataracts, osteoporosis, hypertension, psychiatric disorders, gastrointestinal (GI) ulceration, infections, and other cushingoid symptoms. Therefore, GCs are associated with the treatment of active CD but are not recommended for long-term treatment (1-3). Budesonide is a second-generation GCs that binds to the intracellular GCs receptor with high affinity, exhibiting strong anti-inflammatory effects at the site of inflammation, allowing for local selective treatment of GI tract. Extensive (90%) systemic metabolism in the pre-small intestine and liver mucosa results in low systemic availability. By acting locally and minimizing systemic exposure, oral budesonide preparations offer broadly similar efficacy as systemic GCs but have a better safety profile (1-5). Meta-analyses based on these trials have shown that oral budesonide is more effective than mesalazine or placebo when used for induction of remission in mild to moderately active CD with no difference in side effects (6,7). A cataract is an opacity of the lens of the eye that may cause blurred or distorted vision, glare problems, or, in very advanced cases, blindness. Posterior subcapsular cataracts involve the area immediately anterior to the posterior capsule. They are acquired, in many cases, secondary to GCs therapy or ionizing radiation (8-10). In the literature review, no cataract development associated with oral budesonide has been reported, except for the case of a child with asthma who developed a cataract related to the use of inhaled budesonide therapy (11).

CASE
The presented case is an 18-year-old male patient. There were known previous tonsillectomy and adenoidectomy operations. In addition, there was a diagnosis of CD with ileal involvement, which was diagnosed 3 years ago. The patient applied to our gastroenterology outpatient clinic for follow-up. The patient complained of occasional

abdominal pain and sometimes dripping rectal bleeding. He also had a complaint of decreased visual acuity for several years. In the physical examination; His general condition was good, and his vitals were stable. In the physical examination; His general condition is good, his vitals are stable, body mass index (BMI) =19. In the systemic examination, there was mild gas distension in the abdomen, there was no evidence of defense or rebound in the abdomen, and external hemorrhoids were observed. Recent blood tests (complete blood count, blood biochemistry, stool, and urine tests) were normal. He was taking mesalazine 4000 mg/day orally and azathioprine 150 mg/day oral treatments. In the ileocolonoscopic examination performed 6 months ago, the disease was in remission. When the patient's archive files are examined; Three years ago, a diagnosis of CD with active ileal involvement was made and budesonide treatment was started. In the 11th week of budesonide treatment, the patient developed complaints of a sudden decrease in visual acuity and paleness in colors. No pathological features were found in neurological examination and cranial imaging (cranial magnetic resonance imaging and tomography). As a result of the requested ophthalmology department consultation; a bilateral posterior subcapsular cataract was diagnosed and, it was recommended to stop budesonide treatment and wear glasses. Surgical treatment was not considered, follow-up was recommended. After the budesonide treatment was stopped, the patient's visual acuity improved somewhat after a few months. The patient told us that his visual acuity improved relatively, but he needed to wear glasses.

DISCUSSION

In the presented case, bilateral posterior subcapsular cataracts occurred during budesonide treatment. No other disease or drug effect findings were found to explain this situation. In addition, visual acuity began to improve after budesonide treatment was discontinued. When the literature was reviewed, no cataract development was reported due to oral budesonide treatment.

GCs are still the most commonly used treatments to achieve remission in the active period of the CD. However, due to the dangerous side effects of traditional GCs, budesonide therapy, which has fewer systemic side effects, has been the first choice treatment to achieve remission. In 1994, a new formulation of GCs, budesonide, was shown to have efficacy equal to prednisolone, with 15 times greater affinity for GCs receptors. Budesonide has the added advantage of high first-pass hepatic metabolism and rapid elimination, resulting in minimal systemic absorption and thus reducing the risk of steroid-induced side effects (4,5).

In the literature, a pediatric patient who developed cataracts under the inhaled budesonide treatment given during an active asthma attack has been reported (11). The prevalence of posterior subcapsular cataracts in young patients receiving inhaled GCs for the treatment of chronic asthma is unknown. In a cross-sectional study, slit lamp examinations were performed on 95 consecutive young patients receiving inhaled beclomethasone or budesonide. No posterior subcapsular cataract was detected. This study suggests that routine screening for posterior subcapsular cataracts is not necessary for this patient population (12).

A steroid-induced cataract is a clinical diagnosis reserved for cases of cataract formation in relation to the dose and duration of GCs drug use. The diagnosis of cataracts is based on characteristic findings of opacity on comprehensive ophthalmic examination (10,13). Treatment for cataracts in children depends on the age of the child and its potential to interfere with vision development. If the cataract is visually significant, management requires the removal of the lens and optical/visual rehabilitation, which is critical to prevent amblyopia. Children with good vision, small opacities, or extra-axial opacities can be treated conservatively (14,15). Cataract was detected before the age of 18 in our patient. Our patient was approached conservatively for the treatment of cataracts, and visual acuity improved with the discontinuation of steroid treatment and the use of glasses, without the need for surgical treatment.

In a large study comparing Budesonide and placebo for achieving remission in CD patients. Discontinuation as a result of adverse events occurred in 8% of budesonide-treated patients and 10% of placebo-treated patients. Most adverse events leading to withdrawal were GI symptoms occurring at similar rates in both treatment groups. Non-GI symptoms leading to discontinuation in the budesonide group included single cases of erythema nodosum, rash, viral infection, chickenpox zoster, Cushing's syndrome, pharyngitis, unwanted pregnancy, and malignant brain neoplasm. Non-GI symptoms leading to withdrawal in the placebo group included three cases of Cushing's syndrome and a single case of alopecia, pruritus, acute urticaria, pulmonary abscess, unwanted pregnancy, arthritis, multiple sclerosis-like symptoms, and cholelithiasis, but no cataract was detected as an adverse effect (1). After achieving remission with induction therapy in CD, randomized trials of oral budesonide maintenance therapy showed only moderate benefit in terms of Crohn's Disease Activity Index (CDAI) scores and time to relapse, as confirmed in a recent Cochrane analysis. (10). Meta-analyses have shown that oral budesonide is more effective than mesalazine or placebo when used for induction of remission in mild to moderately active CD with no difference in side effects (3,6,7).On the other hand, budesonide is not recommended for maintenance treatment in CD in the European Crohn's and Colitis

Organization (ECCO) guidelines. Although budesonide-related side effects are rare when used at low doses and the safety profile is similar to a placebo, it is recommended that non-steroidal options such as thiopurines be preferred (15,16).

In this case report, cataract formation associated with budesonide in CD patients is presented. However, this case report cannot overshadow the low adverse effects of budesonide treatment compared to GCs. Budesonide should be the first choice GCs therapy to achieve remission in CD patients in the active phase, and patients should be closely monitored for side effects.

DECLARATIONS

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Case Report

Primary Sjögren's Syndrome Associated Lymphoid Interstitial Pneumonia: The Enemy In Shadows

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ABSTRACT

LIP is characterized by the interstitial infiltration of lung tissue, especially the interalveolar septum by polyclonal lymphocytes, plasma cells and histiocytes. This clinical entity is known for its association with primary Sjögren's syndrome (pSS). In this case presentation, we aim to provide an overview of the diagnosis and treatment processes with a clinical example of this rarely encountered condition. A 69-year-old female patient was referred to our rheumatology department with complaints of cough, shortness of breath, widespread joint pain and bilateral widespread cystic lesions and ground-glass opacities in her thoracic CT scan. The patient had no comorbidities other than a history of metastatic renal cell carcinoma, for which she underwent a left pneumonectomy five years ago. Serological tests revealed ANA > 1:320 and SS-A (Ro) positivity. Salivary gland biopsy showed lymphocytic sialadenitis. Due to the irregular, widespread peribronchial distribution of the cystic lesions seen on the thoracic CT, pSS-associated LIP was considered. Bronchoalveolar lavage (BAL) fluid was rich in lymphocytes but did not provide diagnostic information. In light of these results, the patient was started on treatment with methylprednisolone at a dose of 0.5 mg/kg/day and hydroxychloroquine. Azathioprine was added after tapering steroid and methylprednisolone stopped at 6 months. 4-9% of pSS patients are confronting LIP and 30% of underlying medical conditions in LIP is pSS. It should be noted that rare but potentially life-threatening lung involvements like LIP can develop in Sjögren's cases, and, as in our case, it may even be the initial presentation. Current results are indicating improvement with glucocorticoid+DMARD treatment, but randomized controlled studies are strongly needed.

Keywords: Sjögren, LIP, interstital, lung

INTRODUCTION

Lymphoid interstitial pneumonia (LIP) is a rare type of interstitial lung disease that develops as a result of immune dysregulation and is often associated with rheumatological diseases. LIP is characterized by the interstitial infiltration of lung tissue, especially interalveolar septum, by polyclonal lymphocytes, plasma cells, and histiocytes. This clinical entity is known for its association with primary Sjögren's syndrome (pSS). In this case presentation, we aim to provide an overview of the diagnosis and treatment processes with a clinical example of this rarely encountered condition.

CASE

A 69-year-old female patient was referred to our rheumatology department with complaints of cough, shortness of breath, widespread joint pain, bilateral widespread cystic lesions and ground-glass opacities in her thoracic computed tomography (CT) scan (**Figure 1**). The patient had no comorbidities other than a history of metastatic renal cell carcinoma, for which she underwent a left pneumonectomy five years ago. No chemotherapy or radiotherapy was administered and there was no relapse after five years.

The patient's systemic rheumatological evaluation showed no signs of arthritis, morning stiffness, back pain, Raynaud's phenomenon, photosensitivity, fever, abdominal pain, diarrhea, oral ulcers, genital ulcers, psoriatic rash or erythema nodosum. She also had no history of uveitis, thrombosis or abortions but

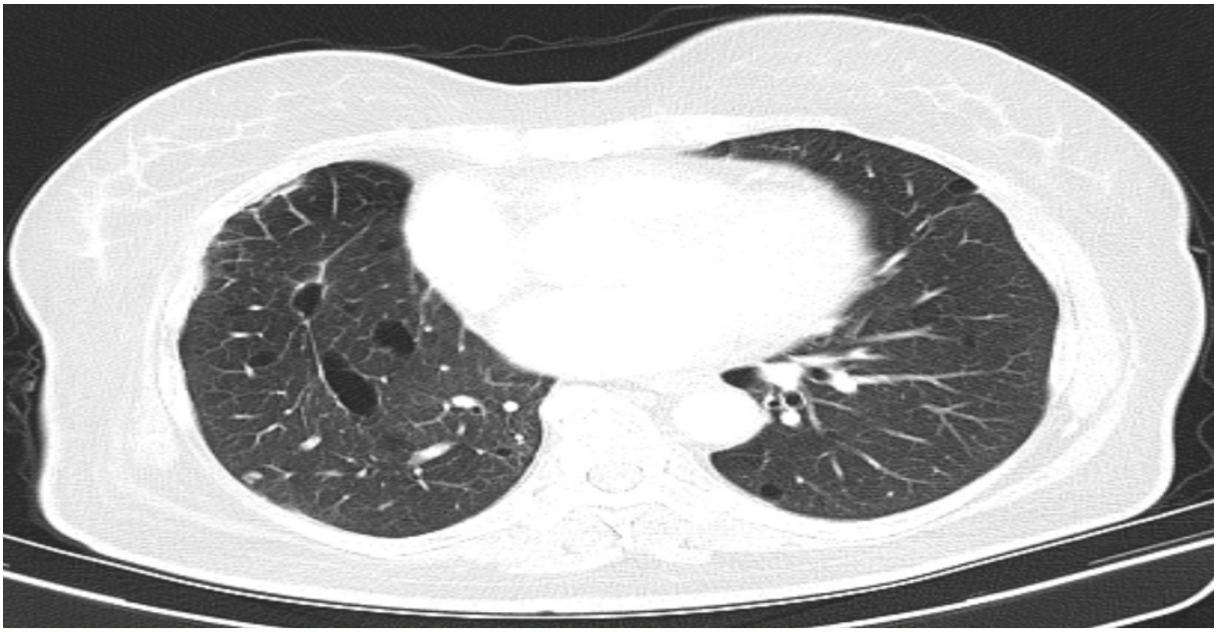

Figure 1. Thin-walled peribronchovascular cysts and ground-glass opacities in CT

complained of severe dryness of mouth not accompanied by dry eyes.

Serological tests revealed ANA > 1:320 and SS-A (Ro) positivity. Schirmer scores were 5 mm for both eyes and salivary gland biopsy showed lymphocytic sialadenitis with focus score 3. Viral panels for hepatitis B/C and HIV were negative and serum protein electrophoresis result was normal. Regarding these findings, pSS diagnose was established according to 2016 ACR-EULAR classification criteria. Due to the irregular, widespread peribronchial distribution of the cystic lesions seen on the thoracic CT, pSS-associated LIP was considered and a lung tissue biopsy was planned. However, due to the patient's history of pneumonectomy and the reduced capacity of the remaining lung, the biopsy could not be obtained. Bronchoalveolar lavage (BAL) fluid was rich in lymphocytes but did not provide diagnostic information.

In light of these results, the patient was started on treatment with methylprednisolone at a dose of 0.5 mg/kg/day and hydroxychloroquine. After 6 weeks of treatment, the patient reported significant improvement in clinical symptoms and the steroid dose was tapered while azathioprine was added to the treatment. Methylprednisolone was stopped after 6 months. Although absence of radiological improvement, the patient experienced amelioration in shortness of breath and complete resolution of cough. She is still under azathioprine and hydroxychloroquine treatment.

DISCUSSION

LIP is characterized by the interstitial infiltration of lung tissue, especially interalveolar septum, by benign polyclonal, mostly mature B or T-cell lymphocytes, plasma cells, and histiocytes. This infiltration can be diffuse or focal and may contain germinal centers, non-caseating granulomas, and multinucleated giant cells (1).

4-9% of pSS patients are confronting LIP and 30% of underlying medical conditions in LIP is pSS (2). It has also been reported in viral infections like HIV, Epstein-Barr virus, chronic active hepatitis or autoimmune conditions such as autoimmune thyroiditis, autoimmune hemolytic anemia, primary biliary cirrhosis, myasthenia gravis. Other rheumatological diseases like systemic lupus erythematosus or juvenile rheumatoid arthritis have also been associated with LIP (5).

The most common clinical symptoms are cough (71%) and dyspnea (61%), but weight loss and fever may also accompany. Due to its slow progression, median time-to-diagnosis was reported as 19 months (3). On thoracic CT scans, thin-walled peribronchovascular cysts associated with ground-glass opacities are observed in up to 80% of LIP cases (4).

Although BAL is crucial for the diagnosis of many interstitial lung diseases, its findings are non-specific for LIP. Therefore, tissue biopsy is mostly mandatory. Video-assisted thoracoscopic surgery or thoracotomy is recommended because transbronchial fine needle aspiration biopsy may not reveal the characteristics of tissue involvement (3).

Regarding treatment, there are no controlled trials in the literature and current guidelines are also not recommend a standardized approach for treatment (5,6). However, data from the literature indicate that the most commonly preferred approach is the addition of glucocorticoids to

disease-modifying antirheumatic drugs (DMARDs) such as hydroxychloroquine, cyclophosphamide, cyclosporine, colchicine and azathioprine. In the study with 15 LIP patients (3), treatment response was evaluated in five out of eight Sjögren's cases. Clinical improvement was observed in three while stable clinical condition was maintained in two. The median overall survival was 11.5 years and three Sjögren's patients were still alive at the end of the follow-up. Although not observed in this study, 5% of LIP patients are under risk of developing lymphoma in the following years (7).

CONCLUSION

It should be noted that rare but potentially life-threatening lung involvements like LIP can develop in Sjögren's cases, and, as in our case, it may even be the initial presentation. Although pneumonectomy history of our case prevented the biopsy, in suitable cases it is critically important for differential diagnose. Current results are indicating improvement with glucocorticoid+DMARDs treatment, but randomized controlled studies are strongly needed.

DECLARATIONS

Ethics Committee Approval Number: Not necessary.
Informed Consent: Informed consent was obtained from patient.
Referee Evaluation Process: Externally peer-reviewed.
Conflict of Interest Statement: Author declares no conflict of interest.

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