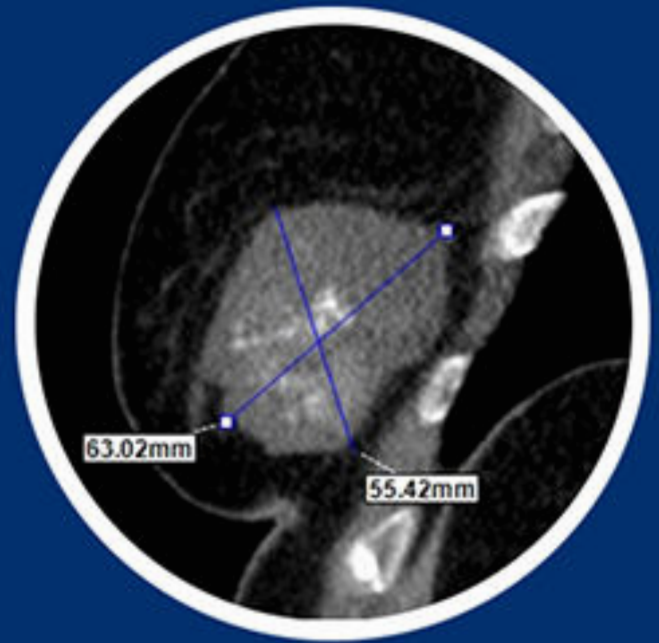
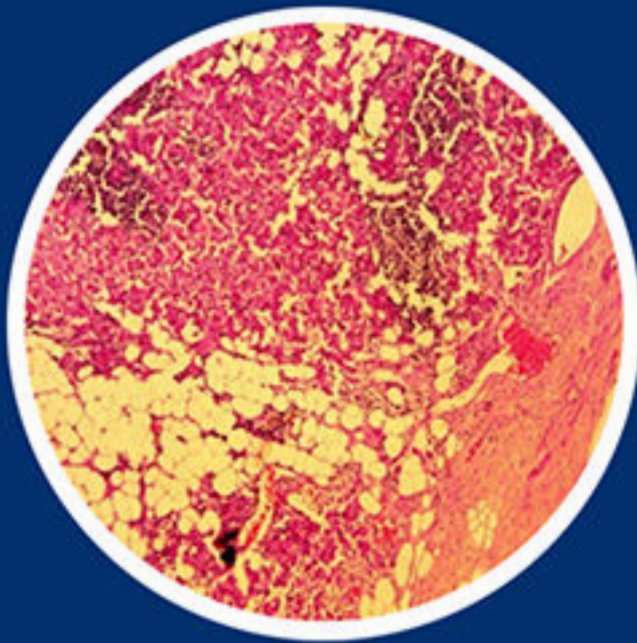


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Comparison of penetrating thoracic traumas in patients with gunshot and stab wounds in an emergency department

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ABSTRACT

Objectives: Thoracic trauma is among the most important causes of mortality in emergency departments. In this study of penetrating stab wounds (PSWs) and gunshot wounds (GSWs) admitted to the emergency department with penetrating thoracic trauma cases clinical findings, emergency treatment approaches and survivals were compared with literature information.

Methods: One hundred fifty-two patients who applied to Bakırköy Dr. Sadi Konuk Training and Research Hospital Emergency Department with penetrating thoracic trauma on 1 January 2014 and 31 December 2014 were evaluated retrospectively the patients. SPSS 22.0, NY, USA program was used in the analyzes.

Results: Patients administered with PSW were 79.6%, with GSW were 20.4%. Patients in the group GSW were admitted to the emergency department with more serious symptoms than patients in the group PSW (Triage level 2, GSW: 87.1%, PSW: 62.8% and Triage level 3, GSW: 12.9% vs. PSW: 37.2%), ($p = 0.010$). Hemothorax (25.8%) in PSW patients and pneumothorax (40.5%) in GSW patients was detected more frequently. Surgical treatment was performed in 14.9% of patients with PSW, tube thoracostomy was performed in 24%, and 62.82% were treated with conservative treatment. Surgical treatment was performed in 35.5% of GSW patients and tube thoracostomy was performed in 29%, and 48.4% were treated with conservative treatment ($p > 0.05$).

Conclusion: Despite the lower incidence of GSW than PSW in emergency departments, GSW require more surgical intervention and have a higher mortality rate.

Keywords: thoracic trauma, emergency, triage, mortality, penetrating

Traumas are among the most important health problems causing mortality and morbidity in the world. Thoracic injuries account for one third of the cases hospitalized with trauma and about 20-25% of traumatic deaths are reported to be due to thoracic trauma [1]. Despite the fact that approximately 70% of thoracic traumas are due to blunt trauma, an important cause of morbidity and mortality is penetrant traumas [2-4]. Most of the patients with thoracic trauma are treated conservatively [5]. Less than 10% of blunt

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chest injuries and only 15% to 30% of penetrating chest injuries require operative intervention (typically thoracoscopy or thoracotomy) [6]. In penetrating thoracic trauma penetrating stab wound (PSW) is still higher than gunshot wound (GSW) although PSW/GSW ratio varies from country by country [7, 8]. Mortality in penetrating thoracic trauma is higher in GSW [7].

In this study, clinical findings of the cases, emergency treatment approaches and survival in emergency department were retrospectively investigated and compared with the literature information in the patients who applied to the emergency department with the cause of penetrating thoracic trauma (PSW and GSW).

METHODS

The study was carried out retrospectively between 01.01.2014 and 31.12.2014 among the patients who applied to Bakırköy Dr.Sadi Konuk Training and Research Hospital Emergency Medical Clinic. Within a year, a total of 158 patient file penetrating thoracic trauma (PSW and GSW) has been reached. Six patients with missing file information were excluded from the study.

The gender of the patients, vital signs, in-hospital emergency triage, thoracic pathologies, injury type, location of injuries, trauma scores, treatment methods, duration of emergency department stay, and mortality rates were evaluate.

This study was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethic Committee.

Statistical Analysis

Mean, standard deviation, median lowest, highest, frequency and ratio values were used in the descriptive statistics of the data. The distribution of the variables is measured by the Kolmogorov Smirnov test. Mann-Whitney U test was used in the analysis of quantitative data. Chi-square test was used to analyze qualitative data, and Fischer test was used when chi-square test conditions were not met. SPSS 22.0, NY, USA program was used in the analyzes.

RESULTS

The age range of the patients was between 15 and 69 years (mean age: 31 ± 11.6 years). Of the 152 patients who were evaluated, one hundred twenty-one were admitted to the emergency department due to PSW and thirty-one of the GSW. There was a male predominance in both groups; 95.9% of PSW patients, 90.3% of GSW ($p = 0.207$). Gender distribution, injury characteristics, treatment, hospital stay, and mortality rates of both groups are summarized in Table 1.

The vital findings of the patients are summarized in Table 2. When the vital signs of both groups were examined, the number of pulses per minute was lower in PSWs (85.8 ± 13.5 / min for PSW, 91.9 ± 14.9 / min for GSW, $p = 0.012$). Percentage of oxygen saturation was higher in PSW group (95.2 ± 9.2 in PSW, 93.8 ± 4.9 in GSW, $p = 0.004$).

Triage severity scores of all penetrating thoracic trauma patients were evaluated in the 2 and 3 categories according to the five-level triage system (67.2% were Triage 2 and 32.8% were Triage 3). Patients in the GSW group had a more severe triage score (Triage 2; GSW: 87.1%, PSW: 62.8%), (Triage 3, GSW: 12.9%, PSW: 37.2%), ($p = 0.010$) than the patients in the PSW group.

In PSW group hemothorax (25.8%) was found and in GSW group pneumothorax was detected more (40.5%). In GSW group, the rates of injury to the right thoracic anterior (32.5%) and right thoracic posterior wall (32.3%) were higher than those in the PSW group ($p = 0.05$ and $p = 0.036$, respectively). When both groups were assessed within themselves, there was no difference in injury location in the GSW group, whereas the most injured location in the PSW group was the left thoracic anterior wall (47.1%).

Both Glasgow Coma Score (GCS) and Triage Revised Trauma Score (TRTS) were higher in PSW group than in GSW group (GCS 14.7 ± 1.6 and 13.6 ± 3.6 , TRTS 11.7 ± 1.6 and 10.7 ± 3.6 , respectively) ($p = 0.007$ and $p = 0.008$, respectively).

Of the patients admitted due to PSW; cardiopulmonary resuscitation (CPR) was performed in 3 (2.5%) patients, tube thoracostomy in 29 patients (24%), mechanical ventilation in 7 (5.8%) patients,

Table 1. Characteristics of the patients

		PSW (n = 121)	GSW (n = 31)	p value
Gender	Female	5 (4.1%)	3 (9.7%)	0.207
	Male	116 (95.9%)	28 (90.3%)	
Triage Level	Triage 2	76 (62.8%)	27 (87.1%)	0.010
	Triage 3	45 (37.2%)	4 (12.9%)	
Injury area	Right tx anterior wall	20 (16.5%)	10 (32.5%)	0.050
	Left tx anterior wall	57 (47.1%)	11 (35.5%)	0.246
	Right tx posterior wall	19 (15.7%)	10 (32.3%)	0.036
	Left tx posterior wall	36 (29.8%)	12 (38.7%)	0.338
Type of injury	Pneumothorax	9 (29%)	49 (40.5%)	0.241
	Hemothorax	8 (25.8%)	22 (18.2%)	0.341
	Lung contusion	5 (16.1%)	14 (11.6%)	0.493
	Rib fracture	4 (12.9%)	17 (14%)	0.869
	Pneumomediastinum	3 (9.7%)	15 (12.4%)	0.676
In the emergency Tube Thoracostomy	Yes	29 (24%)	9 (29%)	0.561
	No	92 (76%)	22 (71%)	
In the emergency Mechanical Ventilation	Yes	7 (5.8%)	4 (12.9%)	0.172
	No	114 (94.2)	27 (87.1)	
Mortality	Yes	4 (3.3%)	4 (12.9%)	0.033
	No	117 (96.7%)	27 (87.1%)	

PSW = Penetrating Stab Wound; GSW = Gunshot Wound, Tx = Thorax

surgical treatment in 18 (14.9%) patients, conservative treatment in 76 (62.8%) patients. Of the patients admitted due to GSW; cardiopulmonary resuscitation (CPR) was performed in 2 (6.4%) patients, tube thoracostomy in 9 (29%) patients, mechanical ventilation in 4 (12.9%) patients, surgical treatment in 11 (35.5%) patients, conservative treatment in 15 (48.4%) patients. Laparoscopy was performed in 4 patients, laparotomy in 8 patients, thoracotomy in 9

patients, sternotomy in 3 patients, laminectomy in 1 patient, AV fistula ligation in 1 patient, arterial repair in 2 patients, foreign body removal in 2 patients and soft tissue repair in 1 patient. The rates of tube thoracostomy (24% in PSW, 29% in GSW, $p = 0.561$) and mechanical ventilation requirement (5.8% for PSW, 12.9% for GSW, $p = 0.172$) were similar in both groups as treatment. Length of stay in the emergency department was 11 ± 8.2 hours in PSWs, and $13.6 \pm$

Table 2. Vital and other findings of patients

	PSW (n = 121)	GSW (n = 31)	p value
Systolic blood pressure (mmHg)	114.3 ± 12.6	114.3 ± 15.6	0.870
Diastolic blood pressure (mmHg)	70.3 ± 9.4	67.5 ± 10	0.160
Pulse (beat/min)	85.8 ± 13.5	91.9 ± 14.9	0.012
Oxygen saturation (%)	95.2 ± 9.2	93.8 ± 4.9	0.004
Respiratory rate (rate/min)	18.2 ± 5.7	18.5 ± 8.8	0.485
Glasgow Coma Score	14.7 ± 1.6	13.6 ± 3.6	0.007
Triage Revised Trauma Score	11.7 ± 1.6	10.7 ± 3.6	0.008
Hospital Length of Stay (days)	11 ± 8.2	13.6 ± 9.8	0.670

Data are shown as mean±standard deviation. PSW = Penetrating Stab Wound; GSW = Gunshot Wound

9.8 hours in GSWs. There was no difference between the two groups in terms of length of stay in the emergency department ($p = 0.670$) (see Table 2).

The mortality rate was higher in GSW group than in PSW group (12.9% in GSW, 3.3% in PSW, $p = 0.033$), although the number of patients who died in both GSWs and PSWs was 4. Of the eight patients who died, six patients had an isolated thoracic injury and there were also abdominal injuries accompanying the thorax in two patients.

DISCUSSION

Thoracic traumas constitute approximately one-fourth of trauma-induced deaths [1, 2]. Thoracic traumas are most commonly seen in males and between the second and fifth decades [9]. In a study of 827 cases of Kong *et al.* [10] comparing penetrating thoracic trauma with PSW and GSW groups, 92% of the patients were male and the mean age was 24. In our study, similarly, 94.7% of the patients who applied for penetrating thoracic trauma were male and the mean age was 31 ± 11.6 . This can be explained by the fact that the young male population plays a more active role in social life and is more exposed to violent incidents.

In Yücel *et al.*'s study [11], 79.2% of penetrating

trauma patients were reported as GSW and 20.8% of them were reported as PSW. In a study of Madiba *et al.* [7] examining penetrating thoracic injuries, 116 GSW patients were seen, compared to 473 PSW patients. In our study, the rate of application for PSW was higher. While these rates vary from country to country in studies, they vary according to the characteristics of the hospital (military hospital, trauma hospital, etc). Due to increased civilian armament rates and terrorist incidents; the increase in the number of patients who are injured by gunshot wounds in the studies conducted is remarkable.

Triage guidelines classify emergency patients into various categories and associate them with the maximum waiting period based on specific clinical emergency criteria. Studies have shown that five-level triage systems are more effective, valid, and reliable [12, 13]. There were no studies about the triage and triage levels of emergency penetrating thoracic trauma and diagnosis and treatment processes. The reason for this may be that the studies were performed by chest surgeons and trauma surgeons in general. Five emergency triage system is applied in the emergency department of our hospital. In this study, there a significant difference in the mortality and treatment duration according to the triage 3 level of the patients diagnosed and treated with triage 2 level and the diagnosis and treatment of the patients with thorax

injuries. Patients in the GSW group had a more severe triage score than the PSW group. It was determined that patients with acute thoracic trauma due to GSW should be evaluated at least triage 2 level in the emergency departments and close follow-up and treatment is required as GSW caused more morbidity and mortality than PSW patients.

The most common intrathoracic complications in thoracic trauma are hemothorax, pneumothorax and hemopneumothorax [9, 11]. In the study of Madiba *et al.*, [7] hemothorax rates were similar in PSW and GSW groups, but the rate of pneumothorax was higher in patients admitted due to PSW. In the study of Kong *et al.*, [10] the rate of pneumothorax was higher in the PSW group, whereas the rate of hemopneumothorax was higher in the GSW group. In our study, hemothorax rate was higher in PSW group, pneumothorax rate was higher in GSW group. In another study conducted in our country, low systolic blood pressure during hospitalization was found to be important for mortality and morbidity [14]. In Hasbahçeci *et al.*'s study [15], low systolic blood pressure and apneic breathing were found to be effective on mortality. In our study; the relationship between mortality, high pulse rate and low oxygen saturation is remarkable in GSW patients with high mortality rates.

It is known that trauma scoring systems are especially important in standardizing trauma severity and predicting prognosis [16, 17]. Eftekhari *et al.* [18] and Champion *et al.* [19] argue that Revised Trauma Score is a predictor of mortality in trauma patients. In the study of Emircan *et al.*, [16] Glasgow Coma Score and Revised Trauma Score of patients with mortality were found to be lower than those of living patients. In our study, GCS and TRTS were lower in GSW group. Glasgow Coma Score and Triage Revised Trauma Score values used in our study were found to be significantly associated with mortality formation in direct proportion to the prevalence and severity of the trauma present in the patient; the importance of using trauma scoring systems in the evaluation of trauma patients.

Conservative approaches without thoracic surgery are often enough in the treatment of thoracic trauma [10, 20]. In particular, it is possible to treat isolated thoracic trauma effectively without surgery and, if necessary, with tube thoracostomy [20, 21]. In the

study of 1142 cases where trauma patients were evaluated, 601 (52%) patients received tube thoracostomy, 38 (3.3%) patient thoracotomy and 503 (44%) patients received conservative treatment [22]. In the study of Kong *et al.*, [10] 96% of the patients were operated without surgery and showed that selective conservative treatment of penetrating thoracic trauma was appropriate. In our study, conservative treatment was applied 62.8% in the PSW group and 48.4% in the GSW group. These ratios are consistent with the literature and show that a selective conservative treatment approach is appropriate for thorax trauma.

The proportion of patients with thoracic trauma requiring major surgery varies between 15 and 20% [23, 24]. In our study, the rate of surgical intervention was 14.9% in patients with PSW and 35.5% in GSW patients. When all patients were evaluated, the rate of surgery was 19%. In the studies performed, the mean hospitalization time of thoracic traumas exceeds 8 days [25]. In the study of Cakan *et al.*, [14] this time was 9.6 ± 8.6 days. The duration of hospitalization in our study was similar to other studies. Approximately 25% of traumatic deaths are due to thoracic trauma [20]. Studies have shown that GSW/ PSW mortality rates are higher [7, 10]. In Clarke *et al.*'s study [26], the mortality rate due to GSW in penetrating thoracic trauma was 8 times higher than the mortality rate due to PSW. In our study, the mortality rate of GSW was found to be higher (consistent with the literature).

CONCLUSION

As a result; patients with GSW in emergency departments require more surgical intervention and have higher mortality although less visible than patients with PSW in emergency departments require. Implementation of in-hospital triage systems is important in terms of patient management and treatment continuity.

Author contributions

NS: study conception, data collection, analysis; DAG: data collection, analysis, manuscript revision; AŞ: data interpretation, manuscript revision; UA: data interpretation, manuscript revision; DNÖ: data interpretation, manuscript revision; All authors have

read and approved the final manuscript.

Conflict of interest

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A review of effective interventions for reducing and controlling obesity in primary school children

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ABSTRACT

Objectives: The prevalence of obesity has been doubled among children over the past 10 years, which will result in an obese population and its complications in near future. This situation can impose great costs on the health system and community for treating those obese people. The purpose of this review is to examine the effective strategies for reducing and controlling obesity in primary school students.

Methods: This review was conducted in August and September 2017. Our goal was to review the related articles in the authorized databases, including Scientific Information Center (SIC), Scholar Google, Scopus, and PubMed, from 2000 onward, by two researchers, considering language constraint (only English articles with full text were accepted). Out of 104,658 articles, 15 articles were excluded due to the lack of full text, and finally 25 articles were selected.

Results: The results of the existing studies showed that through involving parents, schools officials and continuous supporting measures like prohibition of long-term food advertising in television programs, all three educational, nutritional and physical activity interventions can help in controlling and reducing obesity.

Conclusions: To succeed in reducing and controlling obesity among students, especially primary school ones, the approaches and interventions should be implemented in three levels: home, school, and community.

Keywords: Obesity, overweight, community-based program, primary school children, school-based intervention

The prevalence of childhood obesity has increased more than three times in the world over the past 30 years [1]. According to the statistics from 1980 to 2013, the prevalence of obesity among children has increased by 47.1% worldwide [2]. Previously, the problem of obesity and overweight was only for high-income countries, while the problem is rising in low and middle-income countries too, especially in urban areas that are facing nutrition transition and reduced physical activity [3-5]. Nutrition transition is generally

associated with increased consumption of high energy and low fiber food, sweetened drinks, reduced physical activity and a more sedentary lifestyle [6]. A wide range of behavioral and environmental factors contribute to prevalence of obesity, including fast foods consumption, decreased physical activities due to watching TV, using computers and other electronic entertainments, increased consumption of high-calorie food products, and increasing sedentary jobs [7]. Iran, like many other developing countries, has experienced

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overweight and obesity in recent years, due to decreased physical activities and nutritional patterns changes [8]. According to National Integrated Micronutrient Survey (NIMS) study in 2011, overweight and obesity were reported in 7.9 and 5.6 % of 6 year old children, respectively [9]. Also, the prevalence of overweight among 7-10 and 11-14 year old children were 8.2 and 10.2%, and obesity was 11.1 and 12.2%, respectively [10].

Children's obesity is associated with increased psychological factors such as low self-esteem, social alienation, risk of metabolic syndrome, high blood pressure and type 2 diabetes in adolescence. In addition, an obese child is more likely to become an obese adult [6, 8], so that more than 80 percent of adults with obesity, have been overweight in childhood and adolescence [11]. It is difficult to change the behavior in adulthood, so, prevention and control of obesity in childhood and adolescence will be more effective in preventing obesity and its complications in adulthood [12]. Some school-based interventions on children between 6 and 12 years old showed a positive effect on the prevalence of overweight or obesity [12, 13]. Periodic interventions, preferably for 3 years, and parent involvement as a primary intervention target, can help in reducing obesity [14]. Although schools are known as an ideal environment for obesity prevention, systematic reviews and meta-analysis have shown different outcomes regarding the effectiveness of school-based interventions for the treatment and prevention of obesity in children [15]. The results of a study in Korea has shown a school-based obesity control program based on behavior modification and self-efficacy can be effective in decreasing obesity and increasing diet's self-efficacy [16]. Several studies have concluded that school-based interventions, with diet and physical activity can prevent overweight among children in long term, while physical activity interventions, especially in elementary schools, may be more effective in preventing overweight among children in the short term [15].

Therefore, the assessment of such studies plays an important role in identifying and controlling the risk factors associated with obesity in children. This study aimed to identify the best programs and interventions in students of elementary schools in order to control and reduce the incidence of obesity.

METHODS

This review study was conducted in August and September of 2017. In this review, the stakeholders' perspectives and interventions have been studied in three fields of education, physical activity and nutrition, for controlling, reducing and preventing of obesity among children of primary schools in three levels of school, family and society.

Relevant literature in English was identified through electronic search of papers published from 2000 onwards, in SID, scholar Google, Scopus and PubMed. The articles were reviewed by two reviewers. The Keywords used in the research were obese, weight, overweight, primary school children, control, prevent, intervention, control obesity in elementary school children, control of obesity among primary school children, intervention and control of obesity among elementary school children, and intervention and control of obesity among primary school children. Our search was limited to include entries from 2000 to 2017. The searches yielded 104,658 articles. 13 articles were excluded because they did not have full text. Finally, 25 articles were included (Fig. 1).

RESULTS

The selected topics were categorized into 5 groups: (1) Physical activity interventions, (2) School-based interventions for obesity prevention, (3) Education-based and physical activity interventions for preventing obesity (With emphasis on nutrition in schools), (4) Nutrition education-based and physical activity interventions for obesity prevention, and (5) Nutrition-based and physical activity interventions to prevent obesity.

1. Physical Activity Interventions

In the study of Donnelly *et al.* [17], that examined the promotion of physical activity for weight loss and obesity in children over 3 years, the results showed that there was significant difference in BMI in the intervention group compared to the control group. Of course, schools with more than 75 minutes per week of physical activity had fewer increases in BMI than

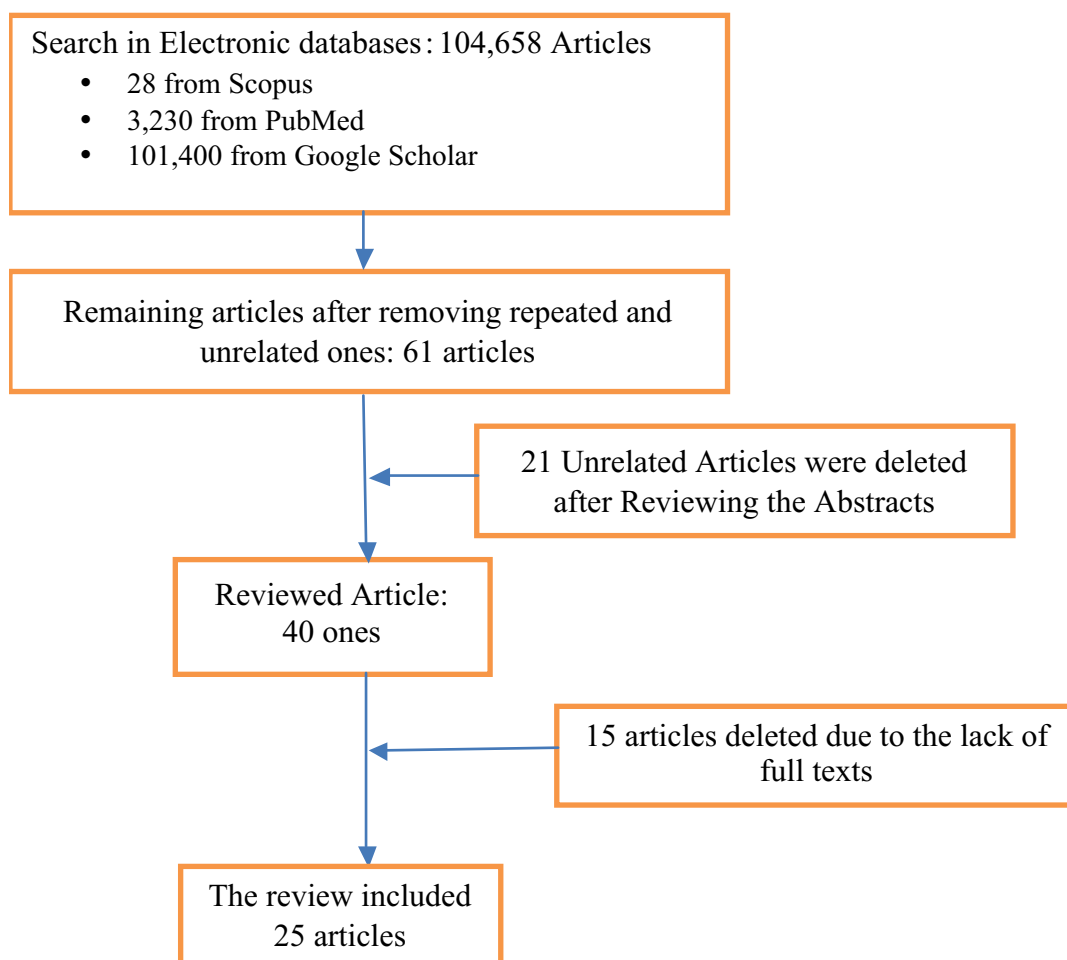


Fig. 1. Flow chart showing the process of screening and selecting the appropriate articles.

schools with less than 75 minutes per week.

In another study, Elizondo-Montemayor *et al.* [18] showed that physical activity in times out of school (3 days per week and 90 minutes each session) did not affect the BMI, and there was no significant difference in the BMI of the intervention and control groups. However, the percentage of skin fold and body fat percent significantly decreased in both girls and boys.

Yin *et al.* [19] studied the effects of an obesity program based on a "fit kid" exercise program without a dietary energy limitation for 3 years. In that program, physical activity intervention included 80 minutes of physical activity appropriate for children who routinely attended in daily school program and the out-of-school program included 120 minutes, 40 minutes for eating snacks, 40 minutes for home works and 40 minutes for physical activity (on holidays without home work, 80 minutes for physical activity). The results of that study showed that percentage of body fat decreased and cardiovascular and pulmonary

function improved in the intervention group compared to control group in the first and second years, but did not have any significant effect on cholesterol (LDL and HDL) and BP levels.

Kriemler *et al.* [20] assessed the result of a one-year survey in a multicomponent physical activity program that included the three compulsory weekly physical activity programs (3 times a week and 45 minutes each time) and the two additional weekly programs (2 times in every two days in week and 45 minutes each time), and in addition, three to five short activity programs (two to five minutes each day) during break times. These physical activities included motor skill tasks such as jumping or balancing on one leg, power games, or coordinative tasks. The result of that study showed that this multidisciplinary intervention improved fitness, reduced fat accumulation, and improved aerobic performance. Also, severe and moderate physical activity increased in school and also in overall physical activity,

similarly. Z scores did not change significantly for everyday physical activity and for the quality of physical and psychological patterns of life.

2. School-based Interventions for Obesity Prevention

In a study by Cawley *et al.* [21] who examined the effect of physical activity training on obesity among obese adolescent school children, showed a reduced BMI Z-score and likelihood of obesity among primary school students, especially boys, with increase in the duration of physical activity classes.

Lynch *et al.* [22] implemented the standard curriculum of 0-1-2-5 (with the goal of consuming 0 sugar-containing drinks, including soda, juice, and sport drinks, participate in at least 1 hour physical activity, limit recreational times to 2 or fewer hours and eating 5 servings of fruits and vegetables) in second and third grade students, over a four-month period. Results of that study showed that there was no statistical difference in improvement of healthy habits, BMI or physical activity in the intervention group compared to the control one.

In Toruner and Savaser study [23] that performed educational interventions (parents and students training on improving diet and exercise habits, increasing physical activity outside of school and reducing TV watching and computer games) on obese and overweight students over a 2.5 month period, it was shown that body mass index (BMI) after 1 year of study significantly decreased in intervention group compared the control group ($p < 0.05$).

Fairclough *et al.* [24] performed the training-based interventions within 20 weeks, as educational class for teachers, parents and students, including healthy life, time and types of effective physical activity, the effect of technology on health and life, balancing energy and carbohydrate and sweet drinks consumption, fight with the hidden fat, increasing the consumption of fruits and vegetables, having high value breakfast, and reducing unhealthy food and snacks. The results of that study showed that BMI and waist circumference decreased, fruits and vegetables intake increased in breakfast meal, and physical activity of students and children's sleep improved.

In Xu *et al.*'s study [25], the results of educational interventions, including healthy eating and appropriate physical activity, school support, family participation

and amusement programs like health classes for parents and children showed there was no significant difference in the BMI of the intervention group compared to the control group; but in the intervention group, decreased BMI about 0.5 kg/m² or more, increased distance of running, decreased watching TV and computer use, decreased consumption red meat, walking instead of using a car or service, compared to the control group were seen.

In a study by Fernandes *et al.* [26], the results of educational interventions -eight educational meetings for 84 minutes on healthy diets, how to make healthy snacks, Pyramid of foods and food groups training, physical activity through games, reading poetry, photography and painting, puppet shows and group plays- showed the percentage of overweight/obese students in intervention groups increased from 21.8 to 23.6% and in non-interventional groups increased from 33.7 to 35.0% ($p > 0.05$). The intervention group significantly reduced the intake of artificial juice ($p = 0.013$) and law-prohibited foods. In the control group, there was a significant increase in prohibited foods intake, such as salty snacks ($p = 0.021$) and freeze foods ($p = 0.031$). Also, intake of breakfast cereal and school snacks decreased ($p = 0.039$).

In the study of Stock *et al.* [27], the results of education-based interventions (Teacher training for older students, and also training of younger students by older ones, 2-3 hours a week for 21 weeks on nutrition, physical activity and healthy body image) showed increase in healthy-living knowledge, behavior, and attitude scores in both older and younger intervention students and a smaller increase in systolic blood pressure, compared to the control group. BMI and weight increased less (in 4th through 7th grade) and height increased more in the younger intervention students (students of kindergarten through 3rd grade). The knowledge not only improved in older students, but also in younger ones. It also led to a slower rate of weight gain among older students.

3. Education-based and Physical Activity Interventions for Obesity Prevention (with emphasis on nutrition in schools)

Of the selected papers in the five studies, nutritional education interventions have focused on school nutrition (buffet, lunch, etc.) and physical activity, simultaneously.

In a study by Hollar *et al.* [28], the results of the interventions including diet-based ones (breakfast, lunch and snacks with an emphasis on the consumption of more vegetables, whole grains and reduced trans fatty acids), education-based ones (school officials or managers, teachers and food providing officials) and increased physical activity (at least 150 minutes per day in the first year, more than 1000 steps per day for the second year, and 5 to 10 minutes physical activity in the classroom and physical activity outside the school) were assessed over 2 years. Result of this assessment showed no significant change in BMI, but the BMI was lower in the intervention group (4.4%) than in the control group (2.5%). Also, the students in the intervention group were significantly higher in math's scores in each two years.

In a study by Kain *et al.* [29], the results of a 6-month education-based intervention (training for school buffet officials and parents, a school curriculum including informing on healthy food), physical activity (providing more than 90 minutes active physical activity for 15 minutes a day, such as dancing, ping pong, basketball and volleyball) and incentive interventions (awarding students who intake a healthy diet during a day) were investigated. It was shown that these interventions had a positive effect on the obesity indices among boys (BMI z-score, waist circumference, but not on tricep skin fold).

In Going *et al.*'s study [30], the results of over 2 years nutrition-based interventions (food delivery such as nuts, cheese sandwiches, yogurt and non-fat milk, non-sugar biscuits, fresh and dried fruits, juices and sugar-free drinks, providing low-calorie mineral water and low-calorie snacks), strategies to promote the sale of healthy foods such as placing healthy foods in view and installing boards to provide information on healthy food patterns, educational interventions (training teachers, students and buffet operators about the provision of healthy and hygienic foods) and physical activity interventions (90 minutes of weekly sports classes at moderate and severe physical activity levels) showed no significant difference in the two groups, but boys were 17 to 21 percent more active than girls.

Sahota *et al.* [31], evaluated the effectiveness of school-based interventions on reducing risk factors of obesity. They studied 10 primary schools in Leeds that

consisted of 634 711 year old children. They measured outcomes of body mass index, physical activity, diet and psychological state. Interventions of that study included teachers' education, modification of school meals, and development of school practice plans aiming the curriculum, physical education, tuck shops, and playing field activities. The consumption of vegetables in children is one of the main challenges of their diet. Implementation of that program led to a modest increase in the consumption of vegetables in intervention children. The result showed that fruit consumption was lower in obese children of the intervention group than those in the control group, while high sugar foods consumption was higher in overweight children of intervention group than control group. There was no difference in BMI and dieting behavior between the groups.

Bustos *et al.* [32] performed interventions over two years. The intervention modes consisted of nutrition education-based ones (inclusion of nutrition education in the curriculum with the goal of improving healthy eating knowledge and habits, establishing a healthy kiosk by the healthy food delivery, including nuts and sandwiches of fresh cheese with tomatoes, fat free yogurt and milk, milk-based desserts, jelly, sugar-free biscuits, cereals, fresh and dried fruits, juices and sugar free drinks, mineral water and other low-calorie snacks) and providing optimal physical activity through organizing physical education classes by a physical education teacher (70 minutes) which half of that spent on moderate to severe activities. The results showed that implementing these interventions by each other, is more effective than doing them alone, in the control of obesity among 6 to 10 year old children.

4. Nutrition education-based and physical activity interventions for obesity prevention

Of the selected papers, 9 studies were performed three interventions, namely physical training, nutrition and physical activity, simultaneously.

The results of a two-year intervention based on pediatric education (reducing sweetened drinks, increased fruit and vegetable intake), daily physical activity (walking), and healthy lifestyle interventions (encouraging healthy food consumption, increasing activity levels, Children's participation in housework and outdoor games) were assessed by Taylor *et al.*

[33]. The results showed that the BMI in the intervention children was lower than the control group. However, there was no difference in the prevalence of overweight between the two groups. Waist circumference, systolic blood pressure, and consumption of carbonated beverages (67% compared to the control group) had decreased in intervention group. In contrast, the consumption of fruits and non-synthetic juices had increased [33].

The three years study of Tarro *et al.* [34] in three levels of education (using pamphlets and training classes for parents, students and teachers), nutrition (encouraging the use of healthy drinks, vegetables, legumes, fresh fruits and nuts, dairy and fish, and decreasing the consumption of carbonated soft drinks, candy and sweets) and physical activity (walking to school, play ground games, increasing physical activity and playing for 1 hour a day) showed that the prevalence of obesity in the intervention group decreased by 0-36.2% and increased by 2.3% in the control group. Among the boys, BMI z-score decreased significantly.

Kocken *et al.* [35], during two years of study, included nutrition (reduced consumption of high-calorie and high-fat foods and sugar-sweetened beverages, promoting a healthy breakfast, increasing fruit and vegetable consumption), physical activity (reducing television watching and computer gaming/browsing, increasing physical activity at and outside school, daily additional activities for engaging with parents and exercise education), and education (group discussions on healthy nutrition and homework assignments) interventions. The results of that two year study showed that in the intervention group, the students' awareness significantly increased compared to the control group and the duration of inactivity in the intervention group was significantly lower than the control group.

Perman *et al.* [36] were implemented an after-school community-based obesity prevention and intervention program in an elementary school. The school's children with a BMI > 85th percentile, were targeted. The students met the fun physical activities, proper nutritional information, and small group sessions with pediatric psychiatry residents focusing on good choices and proper motivations in life, twice a week, for 90-minute sessions. Findings after the first year of the intervention showed a slowing in the

average rate of weight gain in children. A statistically significant difference ($p = 0.027$) was observed in mean BMI percentile for the targeted children. Based on this study, it seems that school-based preventing intervention conducted by a coalition of community agencies and organizations is a promising and cost-effective approach to reduce the prevalence of obesity among children.

Jansen *et al.* [37] conducted an study to evaluate the effect of a school-based intervention program to reduce overweight. The intervention was a multi-component intervention based on behavioral and ecological models. This intervention was implemented in two fields; educational (classroom instruction on healthy nutrition, active lifestyle and healthy lifestyle choices) and physical activity (three hours per week in exercise classes, 5 hours per week in outside school). The results of that intervention showed that the prevalence of overweight increased by 4.3% in the control group and by 1.3% in the intervention group. No significant effects were found for BMI. Also, the sport skills in the children of the intervention group increased.

Rito *et al.* [38] performed a 6-month period intervention based on education (classes for parents and students by nutritionists, healthy eating counseling for overweight and obese students and encouraging healthy foods), physical activity (at least one hour each day) and nutrition (nutrition education to gain skills and behaviors related to fields such as food preparation, food preservation and storage, social and cultural aspects of food and eating and other consumer aspects, and focus on increasing the consumption of fruits and vegetables and reducing sugary drinks and healthy cooking workshop with the presence of parents and students aimed at encouraging healthy eating). The study showed that the total consumption of fruits and vegetables reached 400 grams per day, fiber consumption increased, the consumption of beverages decreased, physical activity increased and watching TV time decreased to 2 hours per day.

In a multi-centered randomized controlled trial, Li *et al.* [39] aimed to evaluate the possibility and effectiveness of the comprehensive intervention program (combination of nutrition and physical activity interventions) for childhood obesity. In that study, three interventions were contained: nutrition education, physical activity and comprehensive

Table 1. Intervention studies evaluating the effect of interventions on BMI, obesity and other criteria

Author [Ref.]	Study	Intervention	Duration of intervention	Result
Donnelly <i>et al.</i> [17]	Randomized controlled study	75 minutes of physical activity per week	3 years	significant difference in BMI
Elizondo-Montemayor <i>et al.</i> [18]	Randomized controlled trial	Increase physical activity during school hours	10 months	There was no significant difference in BMI but decreased the percentage of skin and body fat percentage in both genders
Yin <i>et al.</i> [19]	cluster randomization design	Increased physical activity during school hours	3 years	Decreased body fat percentage, improved cardiovascular and pulmonary function, no effect on HDL, LDL, BP
Kriemler <i>et al.</i> [20]	cluster randomized controlled trial	Increased physical activity	1 year	Improved fitness, reduced fat accumulation, and improved aerobic performance
Cawley <i>et al.</i> [21]	Cohort	Increased physical activity	1 year	Decreased BMI -z score
Lynch <i>et al.</i> [22]	cluster randomized controlled field trial	Nutrition and physical activity education, decreased computer games and TV watching and nutrition	4 months	There was no significant difference in the improvement of BMI and physical activity
Toruner and Savaser [23]	Randomized controlled trial	Education for modifying food patterns, increasing physical activity and decreasing computer games and TV watching	2.5 months	Decreased BMI
Fairclough <i>et al.</i> [24]	randomized intervention study	Modified food pattern education and physical activity	20 weeks	Decreased BMI and waist circumference, increased fruit and vegetable consumption in breakfast, increased physical activity, and children's sleep pattern
Xu <i>et al.</i> [25]	cluster randomized controlled trial	Healthy food patterns education	9 months	No significant change in BMI, reduced TV watching time and computer games, reduced consumption of red meat, increased mobility and increased running distance
Fernandes <i>et al.</i> [26]	controlled intervention study	Healthy food patterns education	2 weeks	Reducing the use of artificial juices, increasing overweight and obesity in the intervention group compared to control group, increased consumption of mass-produced snacks and soda and reduced breakfast cereal consumption in school in the control group
Stock <i>et al.</i> [27]	pilot study	Healthy food pattern education, physical activity	21 weeks	increase in knowledge, behavior, and attitude scores in healthy-living and a lower increase in systolic blood pressure. Less increase in BMI and weight in the intervention older students and height in the intervention younger students
Hollar <i>et al.</i> [28]	quasi-experimental design	Diet, healthy food patterns training and increased physical activity	2 years	No significant change in BMI, but increase in the scores of the math lesson

Table 1 continued. Intervention studies evaluating the effect of interventions on BMI, obesity and other criteria

Author [Ref.]	Study	Intervention	Duration of intervention	Result
Kain <i>et al.</i> [29]	controlled study	Healthy eating pattern, increased physical activity and encouraging interventions	6 months	Decreased BMI, Z-SCORE and waist circumference
Going <i>et al.</i> [30]	randomized trial	Providing healthy diet, healthy food pattern training and physical activity	2 years	Increased mobility in boys compared to girls
Sahota <i>et al.</i> [31]	randomized controlled crossover trial	Education for lifestyle, food pattern and physical activity modification	12 months	Increasing the consumption of vegetables, reducing the consumption of food in obese children, consuming food or sugar in overweight children, and no significant difference in BMI and diet pattern behavior
Taylor <i>et al.</i> [33]	controlled community intervention	Food and healthy lifestyle education	2 years	Decreased BMI, waist circumference, systolic blood pressure and carbonated beverages consumption and increased consumption of fruits and juices
Tarro <i>et al.</i> [34]	randomized controlled trial	Education and promotion of healthy diet and physical activity	3 years	Reduced prevalence of obesity and decreased BMI Z-score among boys in intervention group
Kocken <i>et al.</i> [35]	randomized controlled	Physical activity, training and promoting a healthy diet, reducing TV watching time and reducing computer games	2 years	Increased student awareness, increased mobility
Perman <i>et al.</i> [36]	Field Trial	Healthy food patterns education, physical activity	1 year	Reduction in weight gain and significant change in BMI
Jansen <i>et al.</i> [37]	cluster randomized controlled	Healthy food patterns and physical activity	One school year	Reduced weight gain, reduced waist circumference and increased athletic skills
Rito <i>et al.</i> [38]	Effectiveness Trial	Healthy food pattern and physical activity education	6 months	Increasing fruit and vegetable consumption per day, increasing fiber consumption and reducing soft drinks, increasing physical activity and reducing TV watching
Bacardi-Gascon <i>et al.</i> [40]	randomized cluster controlled trial	Healthy food pattern education	18 months	Decreased BMI in the first 6 months, but increased BMI and ZSCORE and waist circumference. Abdominal obesity, increased intake of vegetables and fruits, reduced inhibition, and reduced consumption of high fat and salt snacks
Klish <i>et al.</i> [41]	Randomized controlled trial	Food pattern training, physical activity and nutrition	1 year	Increased prevalence of overweight and obesity
Safdie <i>et al.</i> [42]	randomized control trial	Physical activity and nutrition	2 year	Increased consumption of healthy foods, physical activity, and sports information and reduced the incidence of obesity

intervention. A classroom-based intervention (happy 10 program) used to promote physical activity among primary school students. That program consisted of a variety of safe, moderate, age- and space-appropriate exercises that was included 2 times a day, 10 minutes

per time, or 1 time a day and 20 minutes per time. The results showed that the program were accepted by the schools, teachers, and students and its implementation is easy.

In a study by Bacardi-Gascon *et al.* [40],

intervention on three fields was assessed during 18 months: (1) training school board and teachers (three 60-minute sessions by nutritionists and sports professionals for teachers and school officials to discuss about healthy lifestyles, how to improve school meals and snacks in the cafeterias, and how to improve physical activity in school and outside school), (2) improving classroom curriculum (the classroom curricula for 2nd and 3rd grades designed to promote healthful eating behaviors and to increase physical activity like reducing the consumption of beverages and soft drinks, fat and sugar, and increasing fruit and vegetables consumption, increasing physical activity for 30 minutes each week for 8 weeks during the year, reducing screen time, and assessing food consumption and physical activity among children), and (3) parent involvement (the purpose of it, was to inform them of the intervention program and provide nutrition education and to develop their knowledge on healthy lifestyle and eating behavior of parents, which consisted of four 60-minute sessions that were conducted by nutritionists each month during a year). The results showed BMI decrease (-0.82) after six-month, BMI and waist circumference z-score increase after 24 months, and 8% decrease in abdominal obesity and 18% increase in overweight and obesity. Additionally, increased intake of vegetables and physical activity reduced sedentary activities and consumption of high fats and salts snacks have been reported.

Klish *et al.* [41] performed a study with the aim of determining the effectiveness of a school-initiated cognitive and behavioral program to reduce childhood obesity. The study was conducted on one-year education-based interventions (including 30 minutes of nutrition education, outside school hours, nutrition classes for changing habits such as selecting less volume of drinks and food, children's favorite fruits and vegetables in the daily diet, and playing video on healthy eating and teaching food labels), physical activity (including 30 minutes of physical activity and proper physical activity for cardiovascular health such as jumping, ball games in open space, team games and play in the school environment and after school hours, football, karate and dancing) and nutrition (providing healthy meals and 2-3 fruit snacks in the school). The results of that study showed the prevalence of overweight and obesity was 18.9% and 30.4% versus

19% and 30.2%, respectively, in the intervention and control schools. Also, in the control school, the incidence of overweight increased, but the incidence of obesity, weight, and BMI z-scores increased significantly in the intervention school.

5. Nutrition-based and Physical Activity Interventions to Prevent Obesity

In a two-year study by Safdie *et al.* [42], the results of physical activity-based interventions (including increased physical activity time at school and holding sports classes at resting hours) and nutrition (including increased fruit and vegetables consumption and available mineral water and reducing high-calorie food available) were examined. The results showed that the selection and consumption of healthy foods, physical activity and sports information increased by children and the prevalence of overweight and obesity decreased.

Intervention studies evaluating the effect of interventions on BMI, obesity and other criteria are summarized in Table 1.

DISCUSSION

The purpose of this review was to answer the question whether implementing single interventions such as increasing physical activity, nutrition education, physical activity and or improving child nutrition behaviors, such as supervision of school buffets for the supply of healthy foods can help to reduce obesity or it is better to implement multidisciplinary interventions.

In the investigating of the effect of physical activity interventions on BMI, one study [17] has shown that physical activity has a significant difference in the reduction of BMI in the intervention group compared to control one, but in another study [18], the change in BMI was not significant in the two groups, but showed significant reduction on skin thickness and body fat percentage in both genders. In another study [19], this intervention reduced the percentage of body fat and improved cardiovascular and pulmonary function among students, but did not show any effect on LDL, HDL, and blood pressure. In another multidisciplinary study [20] that compulsory physical activity was included, the results indicated

improved fitness, reduced fat accumulation and improved aerobic performance. All in all, it seems that interventions on the weight and BMI status have different and unpredictable effects. Seven studies have been done on the effects of education on nutrition and nutritional habits, increased physical activity and healthy lifestyle. One study [21] showed that physical activity education reduced BMI z-score and reduced the likelihood of obesity among 5th grade elementary students, especially boys. In 5 studies [22, 24-27], it was also shown that educational intervention in a relatively short time period (2.5 to 4 months) does not have an effect on the reduction of obese students' BMI. But a study [23] showed that continuous training for parents and students on improving diet habits, increasing physical activity and reducing the time of watching television and computer games, after 1 year, resulted in a significant reduction in children's BMI. In general, the implementation of these types of interventions concluded that educational programs for students, parents and school officials could have a positive impact on the weight loss of obese children, if they were continued and in the long term (at least one year). Other interventions that have considered both increasing physical activity and education as two effective strategies, have shown the greater impact of these multidisciplinary interventions. In these types of interventions, school officials, teachers, students and their parents, food service providers and school buffet operators, trained to provide healthy food products such as non-sugar drinks, milk and lean yogurt, fresh and dried fruits, sugar-free biscuits and low-calorie snacks. In two studies [28, 30], which used more than 90 minute physical activity per day, no significant difference was shown among children.

However, in a similar study [29] which lasted for six months, mixing encouraging interventions (awarding students who consumed healthy food during one day) with the above-mentioned interventions had a positive effect on BMI and z-score, but not for the thickness of skinfold. It can be concluded from these interventions that physical activity and education alone cannot be effective in decreasing BMI, even in the long term, and it is necessary to consider simultaneous enhancement of children's physical activity and the use of encouraging tools.

Nine studies [33-41] were investigated the

simultaneous impact of education, nutrition and physical activity interventions on weight loss and dietary modification and lifestyle. The results of the studies indicated that the probability of success of these interventions is greater if the multidisciplinary method is used. On the other hand, in the nutritional behaviors and BMI, the duration of the intervention is very important, and accessing to a good outcome is very likely in interventions which last for more than 1 year. In multiple interventions, due to the multiplicity of outcomes, there have been significant improvements at least in one of the three outcomes of increased awareness, nutritional behaviors and weight status.

Two studies were conducted to determine the effect of simultaneous physical and nutritional interventions. In one study [42], these interventions increased physical activity and sports information, increased consumption and choice of healthy foods, and decreased overweight and obesity rates, during two years of implementation. The study showed that direct interventions on nutritional behaviors by providing favorable conditions, improve the studied indicators.

CONCLUSION

In reviewing the implemented programs, the reports show that the schools are very suitable environments for implementing weight control interventions. However, in all the reports, there is almost an emphasis on the need for multidimensional and holistic interventions. Since the school environment exposes all children to interventions, it can also reduce peer pressure, which psychologically prepares children to change. After school, the most important issue is the home and the family, due to the strong emotional relationships, the possibility of inducing correct behaviors and strengthening them. Finally, the socio-cultural context of the society is also at a level that can facilitate change by creating the right conditions for physical activity, the availability of healthy foods, and the provision of appropriate incentive messages.

In general, the following factors can be considered as the most important factors involved in the adoption of healthy behaviors: (1) Training: Includes training

for teachers, coaches, parents, children and school buffet and catering staff, (2) Proper environmental conditions: Healthy buffets in schools; An irritating, refreshing and elegant dining room with an adequate time to eat; Having enough space and time for physical activity; Providing encouragement for healthy behaviors, and (3) Designing an interventional program with the participation of all stakeholders: School administrators, trainers and teachers; Parents and children of around society (Child's social circle).

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Reversal effect of quercetin on talazoparib resistance in *BRCA1* mutant triple negative breast cancer

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ABSTRACT

Objectives: Poly (ADP-ribose) polymerase (PARP) inhibitors have demonstrated an outstanding activity in patients with *BRCA*-mutated and wild-type breast cancer. However, the identification of resistance mechanisms to PARP inhibitors is a significant clinical challenge in effective treatment. Thus, new therapeutic strategies are urgently needed to overcome resistance. The aim of the current study was to explore the potential effect of quercetin on HCC1937 (*BRCA1* mutant) and talazoparib (BMN 673), a PARP inhibitor, resistant HCC1937 (HCC1937-R) triple negative breast cancer cells (TNBC).

Methods: We firstly generated BMN 673 resistance HCC1937 cells by continuous exposure to BMN 673 during 6 months. Then, cells were exposed to the different concentration (0-100 µM) of quercetin and the cytotoxic and apoptotic effects of quercetin on these cells were evaluated by WST-1, Annexin V and dual acridine orange-ethidiumbromide (Et-BR) staining.

Results: The cell viability of HCC1937 and HCC1937-R cells reduced to 37.1% and 44.2% at a concentration of 100 µM, respectively for 48 h ($p < 0.01$). Apoptotic rates of HCC1937 and HCC1937-R cells treated with 100 µM quercetin were nearly 56.0% and 46.0%, respectively ($p < 0.01$). Additionally, theapoptotic morphologicalchanges were observed in these cells.

Conclusions: In conclusion, the obtained results suggest that quercetin could potentially be used as an alternative therapeutic strategy in *BRCA1* mutant TNBC to overcome acquired BMN 673-resistance.

Keywords: Triple negative breast cancer, PARP inhibitors, talazoparib (BMN 673), quercetin, apoptosis, *BRCA1*

Poly (ADP-ribose) polymerase (PARP) inhibitors have shown promising clinical activity in patients with *BRCA*-mutated and wild-type breast and ovarian cancer. Several PARP inhibitors [iniparib, talozoparib, veliparib, rucaparib and niraparib] currently being investigated in late stage (phase II-III) clinical trials and olaparib is currently approved by FDA for the treatment of *BRCA*-mutated breast cancer patients with a deficient homologous recombination (HR) pathway

through synthetic lethality [1-6]. However, recognizing the role of resistance mechanisms (altered HR and nonhomologous recombination (NHEJ) capacity, changes in PARP1 activity, multiple drug resistance (MDR) and epigenetic changes) to PARP inhibitors is a major clinical challenge in successful treatment [7-9].

BMN 673 (Talozoparib) is a novel and the most potent PARP inhibitor in phase II/III clinical trials for

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BRCA1/2 mutation-associated advanced breast cancers due to the potency in PARP-trapping [10-13]. However, some studies have revealed that acquired resistance to BMN 673 is limiting the success of future treatment options [14-16]. Thus, novel approaches are required to restore sensitivity to BMN 673.

Quercetin is a polyphenolic flavonoid widely found in many fruits (apple, blueberries, broccoli, grape, leek), vegetables, nuts, and red wine. Quercetin exerts anti-inflammatory, anti-diabetic, anti-allergic, antiviral, anti-fungal and significant anti-carcinogenic activities. It has been reported that quercetin has a potential anticancer effect in different cancer cell lines (breast, prostate, osteosarcoma, colon, gastric, esophageal, ovarian cancer and hepatocellular carcinoma) through the induction of apoptosis both *in vitro* and *in vivo* [17-25]. However, limited studies have shown the reversal effect of quercetin in resistance-cancer cells [26-30].

Here, for the first time, we investigated the reversal effect of quercetin on BMN 673 resistance. This study assessed the cytotoxic and apoptotic effects of quercetin on HCC1937 (*BRCA1* mutant), BMN 673-resistant HCC1937 (HCC1937-R) triple negative breast cancer (TNBC) and MCF-10A human mammary epithelial cell lines.

METHODS

HCC1937 and MCF-10A were purchased from ATCC (Manassas, VA, USA). HCC1937 and HCC1937-R cells were cultured in 5% CO₂ at 37°C in RPMI medium supplemented with 10% fetal bovine serum (FBS) and 100 U/ml penicillin and 10 mg/ml streptomycin. HCC1937-R cells were generated by continuous exposure to 0.01 nM BMN 673 during 6 months. MCF-10A cells were grown in Dulbecco's Modified Eagle Medium: Nutrient Mixture F-12 (DMEM/F-12) medium supplemented with 100 mg/ml EGF, 1 mg/ml hydrocortisone, 10 mg/ml insulin, 10% FBS, penicillin and streptomycin (100 units/ml) at 37° in a humidified atmosphere.

WST-1 Assay

HCC1937, HCC1937-R and MCF-10A cells were seeded at a density of 2x10⁴ cells per well in 96-well plates. After overnight incubation at 37°C, the cells

were treated with different concentration of quercetin for 24 and 48 hours. At the end of the treatments, 10 µl WST-1 dye (Biovision, USA) was added to every single well and plates were incubated for 1-3 hours at 37°C. Finally, the cell viability was measured at 450 nm with a microplate reader (Tecan, Switzerland).

Annexin V and Dead Cell Assay

The apoptotic effect of quercetin on HCC1937 and HCC1937-R cells was determined by Annexin V and Dead Cell kit (Millipore, Germany). After treatment with different concentrations (12.5, 25, 50 and 100 µM) of quercetin for 48 h, the collected cells were rinsed with sterile phosphate-buffer saline (PBS). For each sample of cells, 100 µl MUSE Annexin V and dead cell reagent was added and subsequently incubated for 30 min at room temperature. Finally, the cells were analyzed using a Muse Cell Analyzer

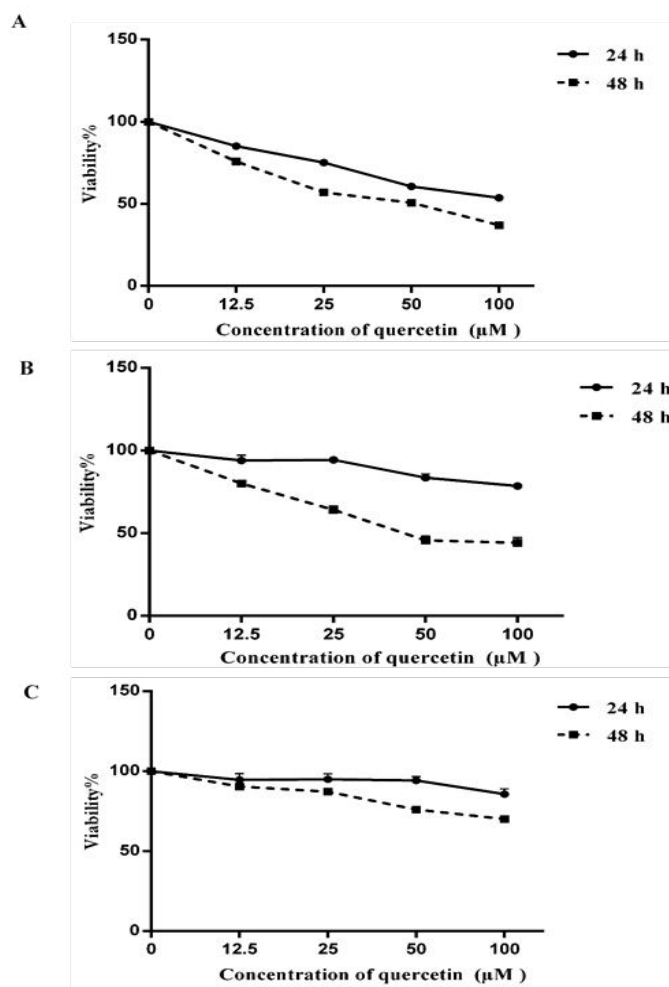


Fig. 1. The cytotoxic effects of quercetin as measured by WST-1 on (A) HCC1937, (B) HCC1937-R and (C) MCF-10A cells for 24 and 48 h. Data are the means of triplicate experiments; error bars, SD ($p < 0.05^*$, $p < 0.01^{**}$).

(Muse™ EMD Millipore Co., Hayward, CA, USA).

Dual Acridine Orange (AO)/Ethidium Bromide (Et-BR) Staining

The morphological changes in quercetin-treated HCC1937 and HCC1937-R cells were observed by AO/Et-BR double staining. A total of 5×10⁵ HCC1937 and HCC1937-R cells were seeded in 6 well plates and treated with 12.5, 25, 50 and 100 μM quercetin for 48 h. At the end of the treatments, the cells were fixed in 4% paraformaldehyde (Merck, Germany) for 30 min. After fixation, the cells were rinsed three times with PBS. Subsequently, the cells were stained with AO/Et-BR solution (Sigma, USA) and observed under an EVOS FL Cell Imaging System (Thermo Fisher Scientific, USA).

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (SPSS Inc, Chicago, IL, USA). All data analyzed were presented as mean value ± standard error of mean (SEM) (n = 3). A one-way analysis of variance (ANOVA) with post-hoc Tukey was used for comparison of multiple variables. *p* - value of < 0.05 was regarded as statistically significant (**p* < 0.05, ***p* < 0.01).

RESULTS

Cytotoxic Effect of Quercetin in TNBC

The cytotoxic effect of UA on HCC1937, HCC1937-R and MCF-10A cells was assessed using

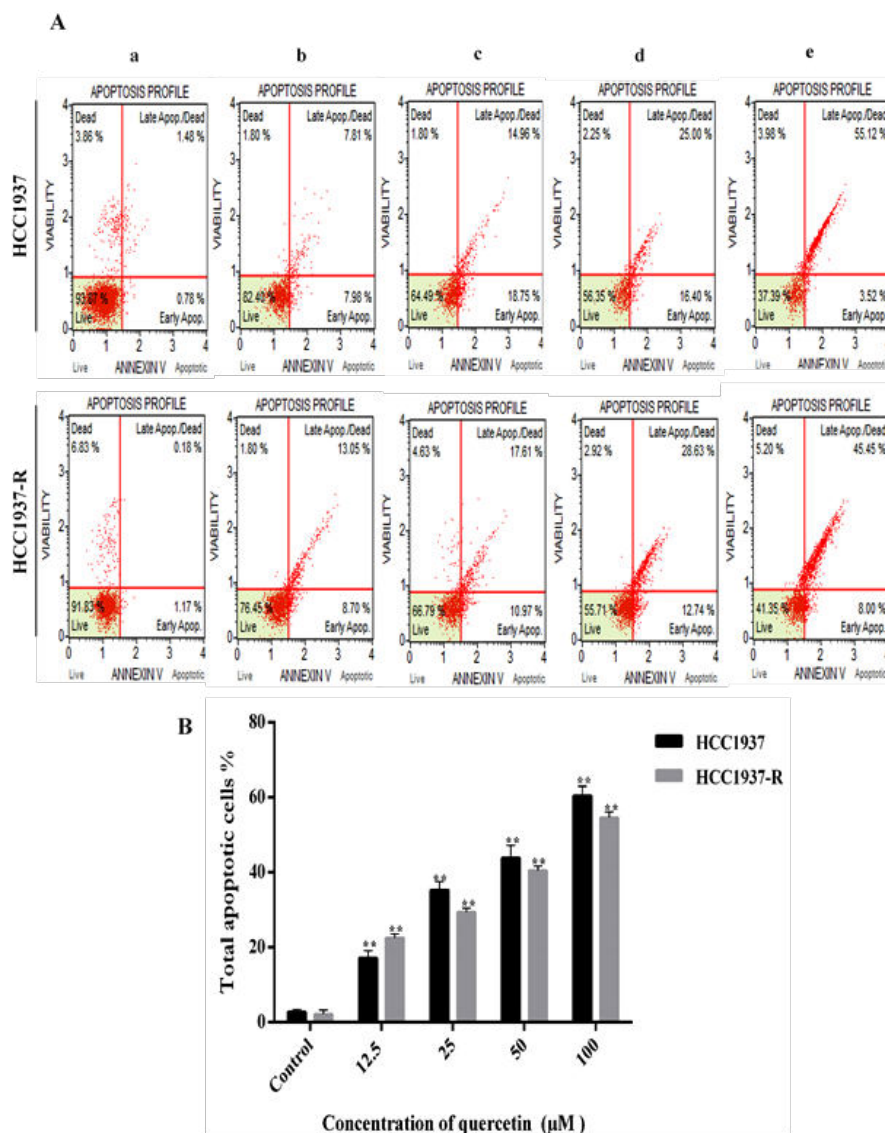


Fig. 2. The apoptotic effects of quercetin on triple negative breast cancer cells for 48 h. (A) HCC1937 and HCC1937-R cells were treated with (a) Control, (b) 12.5, (c) 25, (d) 50 and (e) 100 μM quercetin, respectively. (B) A statistical graph of total apoptotic cells after treatment with different concentration of quercetin (**p* < 0.05, ***p* < 0.01).

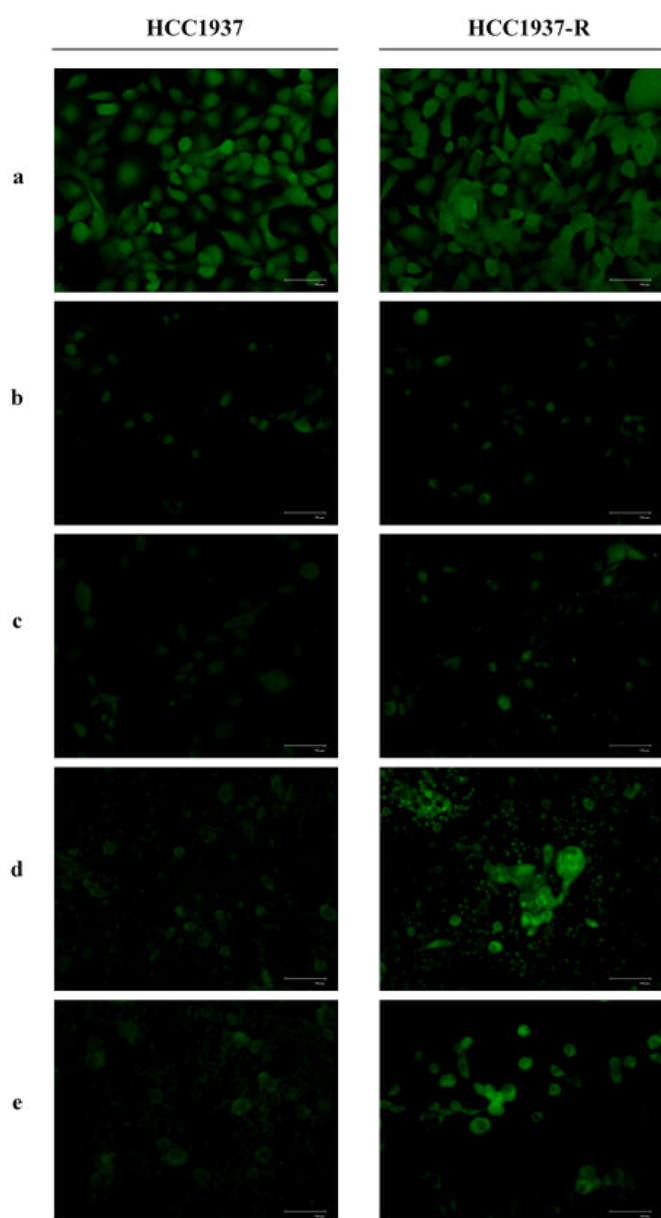


Fig. 3. AO and EtBr double-staining of HCC1937 and HCC1937-R cells following treatment with (a) Control, (b) 12.5, (c) 25, (d) 50 and (e) 100 μM quercetin, respectively for 48 h.

WST-1 assay as shown in Fig. 1. The HCC1937, HCC1937-R and MCF-10A cell viability decreased by 53.7%, 78.5% and 85.8%, respectively at concentration of 100 μM for 24 h ($p < 0.01$). After 48 h incubation, quercetin significantly reduced the HCC1937, HCC1937-R and MCF-10A viability to 37.1%, 44.2% and 70.2%, respectively at 100 μM ($p < 0.01$). The IC_{50} values for quercetin in HCC1937 and HCC1937-R cells were 52.9 μM and 44.2 μM , respectively. As a result, quercetin had a considerable cytotoxic effects on HCC1937 and HCC1937-R cells and quercetin could potentially overcome BMN 673-

resistance. Additionally, no toxic effects were observed with doses lower than 25 μM for 48 h in MCF-10A cells.

Apoptotic Effect of Quercetin in TNBC

The apoptotic effect of quercetin on HCC1937 and HCC1937-R cells for 48 h was determined by Annexin V analysis and the results were summarized in Fig. 2. The percentage of late-apoptotic cells was $7.81 \pm 1.9\%$ and $55.12 \pm 2.8\%$ at 12.5 and 100 μM of quercetin, respectively compared with control ($1.48 \pm 0.7\%$) in HCC1937 cells. Furthermore, the percentage of late-apoptotic cells increased from ($0.18 \pm 0.4\%$) to $13.05 \pm 1.0\%$ and $45.45 \pm 1.7\%$ at 12.5 and 100 μM , respectively in HCC1937-R cells. Thus, quercetin significantly induced apoptotic death in HCC1937 and HCC1937-R cells in a dose-dependent manner ($p < 0.01$).

Morphological Observations

To investigate the morphological changes in HCC1937 and HCC1937-R cells, AO/EtBr staining was performed as summarized in Fig. 3. AO/EtBr staining revealed a dose dependent apoptotic cell death in HCC1937 and HCC1937-R cells when exposed to quercetin for 48 h. Quercetin induced nuclear condensation, cellshrinkage and rounding and membrane blebbing in these cells. These findings were confirmed by WST-1 and Annexin V analysis.

DISCUSSION

In the current study, we investigated the effect of quercetin on the reversal of BMN 673-resistance in TNBC cells. Our results demonstrated that quercetin could potentially reverse BMN 673-resistance and exerted therapeutic effects on HCC1937 and HCC1937-R cells through induction of apoptosis. PARP inhibitors have attracted attention in pre-clinic and clinic to treat particularly *BRCA1/2* mutant breast and over cancers due to inducing synthetic lethality. Three PARP inhibitors (olaparib, rucaparib, and niraparib) have now been approved by the FDA for patients with BRCA-mutated ovarian cancer [5, 31, 32]. Additionally, The FDA has also approved olaparib for patients with *BRCA*-mutated breast cancer. However, phase II/III trial of olaparib and iniparib

failed to show an improvement in disease-free survival and/or overall survival (5.7 months) and significant clinical responses in patients with TNBC [33-36]. Thus, novel PARP inhibitors including BMN 673 [13], niraparib [37], rucaparib [38] and veliparib [39,40] which exhibit synthetic lethality in patients with *BRCA1/2* mutation have gained considerable attention.

In vivo and in vitro studies of BMN 673 demonstrated excellent efficacy against breast, non-small cell lung, chronic lymphocytic leukemia (CLL), prostate, endometrial and ovarian cancer cells [10, 11, 41-44]. However, there are now several studies in the literature stating that particular resistance mechanisms could affect the clinical successes of PARP inhibitors [8, 9, 45-48]. Previous studies from our lab demonstrated that HR and multi-drug resistance (MDR) mechanisms played a major role in the development of resistance to BMN 673. Besides, we found that HCC1937-R cells was almost 3.0-fold more resistant to BMN 673 than HCC1937 parental cells [49,50]. Therefore, development of new treatment strategies to overcome resistance are important for clinical utility of PARP inhibitors.

Quercetin, a polyphenolic compound, has been shown to induce cytotoxicity and apoptosis in different cancer cells. Quercetin induces apoptosis in cancer cell lines by the intrinsic pathway due to interaction with DNA directly [18-20, 23-25]. Furthermore, it has been reported that quercetin could overcome the acquired resistance to chemotherapeutic agents (tamoxifen, 5-FU and enzalutamide) [26, 28, 30]. For this purpose, the multi-drug resistance reversal activity of quercetin was evaluated in the current study. Our results showed that quercetin remarkably decreased proliferation and induced apoptosis in HCC1937 and HCC1937-R cells. These effects were enhanced with increasing concentration and exposure time of quercetin. However, we found no significant reduction in MCF-10A cell viability even at the lowest concentration for 48 h or short-term exposure (24 h) of quercetin.

Furthermore, previous report demonstrated that quercetin displayed PARP inhibitory effects through synthetic lethality to *BRCA2*-deficient cells and induced significantly DNA damage on V79 Chinese hamster lung wild-type cells, its *BRCA2* mutant (V-C8) and genetically complemented mutant with human

BRCA2 (V-C8 hBRCA2)[51,52]. Thus, one of the possible mechanism is quercetin can interfere with DNA and may be able to overcome BMN 673 resistance thanks to its PARP inhibitory effect. However, the underlying mechanisms towards overcoming BMN 673 resistance should be explored. The preliminary results indicated that quercetin could be a potent candidate and reverse BMN 673 resistance.

CONCLUSION

In conclusion, the present study indicated that quercetin had a potential flavonoid to reverse BMN 673 resistance by inducing apoptosis. However, quercetin-induced synthetic lethality and associated mechanisms (homologous recombination, non-homologous recombination and multi-drug resistance) in *BRCA1* mutant TNBC cells should be elucidated by in vitro and in vivo experiments.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Effects of exercise-based cardiac rehabilitation on heart rate variability and turbulence in patients with ST elevation myocardial infarction

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ABSTRACT

Objectives: The objective of this study was to evaluate the effect of the exercise-based cardiac rehabilitation (CR) on the heart rate variability (HRV) and turbulence (HRT) in patients with ST elevation myocardial infarction (STEMI) treated with the primary percutaneous coronary intervention (PCI).

Methods: One hundred one patients with STEMI, who underwent primary PCI were included in our study. Sixty-eight of these patients were randomized to the CR group and the remaining 33 patients to the control group. One month after the primary PCI, cardiac rehabilitation was performed in CR group with a cycle ergometer for 8 weeks (30 sessions). One month after STEMI, rhythm Holter monitorization was carried out in both groups for 48 hours. The rhythm Holter monitorization was repeated in cardiac rehabilitation group (CR group) after the cardiac rehabilitation again for 48 hours. HRV was evaluated according to time and frequency domains; HRT was evaluated with the turbulence onset and turbulence slope parameters obtained from the Holter recordings.

Results: Baseline characteristics and baseline HRV and HRT parameters were comparable between CR group and control group. In CR group, there was no statistically significant difference between the HRV and HRT parameters, which were obtained before and after the cardiac rehabilitation. The subgroup analyses (left ventricular ejection fraction lower or higher than 40%) showed that turbulence onset improved with the cardiac rehabilitation in the group with an ejection fraction lower than 40%.

Conclusions: Our results showed that exercise-based cardiac rehabilitation did not affect HRV and HRT in patients whose left ventricular ejection fraction was mildly affected (> 40%) after the treatment with primary PCI. However, the cardiac rehabilitation provided an improvement of turbulence onset in patients with the low left ventricular ejection fraction.

Keywords: Cardiac rehabilitation, ST elevation myocardial infarction, heart rate variability, heart rate turbulence

The cardiac rehabilitation (CR) can be defined as the whole of the activities, which are necessary for the patients with cardiovascular diseases to restore the premorbid physical, mental and social skills as quickly as possible [1]. Several studies documented

the efficacy of the exercise-based CR after diffuse myocardial infarction (MI). The exercise improves concurrently the physical performance, muscle strength; dyspnea and angina symptoms and a comprehensive CR implementation are related to the improvement of

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the psychological and social functions, going back to work and biological risk factors.

It is well known that the balance between the sympathetic tonus and vagal tonus is changing in favor of sympathetic tonus after the MI. The CR decreases the risk of sudden death as a result of the increase in the fibrillation threshold depending on the increase in the vagal tonus [2]. The autonomous function disorders of the cardiac system have an important place in the pathophysiology of the malign arrhythmias and sudden cardiac death (SCD) [3]. It was reported that after the ischemia and infarction, the parasympathetic tonus decreases along with the decrease of the ventricular fibrillation (VF) threshold due to the increased catecholamines [4]. Heart rate variability (HRV) and heart rate turbulence (HRT) are tests related to the cardiac autonomous functions. HRV shows the effects of the parasympathetic and sympathetic systems on the heart rate. After a ventricular ectopic beat, the sinus rate first increases and then decreases. HRT is used to investigate this phenomenon. It is a reliable indicator of the baroreceptor sensitivity [5, 6]. HRT is evaluated with these two parameters: Turbulence onset (TO) and the turbulence slope (TS). The European Society of Cardiology stated that HRV is a reliable indicator of the vagal activity and is an independent indicator of the total mortality [7]. Likewise, our objective was to evaluate the effect of the CR on the cardiac autonomous functions with the help of the HRV and HRT parameters in ST elevation myocardial infarction (STEMI) patients.

METHODS

Patient Selection

One hundred one consecutive patients, who had applied to the Bursa Yüksek İhtisas Training and Research Hospital and had been admitted with the diagnosis of STEMI in 2014, were included in the study. Their ages ranged between 35 and 85 years and all had undergone primary PCI. In 68 of these patients, CR was performed at least one month after the primary PCI. The remaining 33 patients formed the control group. Patients, who had serious valve disease, had an age over 85 years, respiratory function disorders, decompensated heart failure, uncontrolled hypertension (HT), diabetes mellitus (DM),

orthopedic disability, previous cerebrovascular disease and did not accept the CR program for different reasons, were excluded from the study. Patients, who did not have a sinus rhythm and had a pacemaker rhythm, were also excluded from the study. The findings in the anamnesis and physical examination, risk factors related to atherosclerosis, demographic characteristics, maximum troponin and CK-MB levels at admission, lipid parameters were recorded. Echocardiographic examination was performed and the obtained data were evaluated according to the guideline of the American Echocardiography Society with the standard technique and the 3.5 MHz phase-adjusted transducer GE Vivid 7 pro device (General Electric Company, Connecticut, USA).

Cardiac Rehabilitation Procedure

The patients, who had STEMI and underwent PCI were included in the 8-week CR program after one month from the intervention. CR was performed with a cycle ergometer for 8 weeks, according to the targeted Watt level and heart rate. The average numbers of sessions per week were 4 and each session lasted approximately 30 minutes (5 minutes warm-up, 20 minutes aerobic exercise, which increased the heart rate up to 70-85% and 5 minutes cool down).

Rhythm Holter Analysis

In both groups, at least one month after STEMI, rhythm Holter monitorization (ELA Spiderview Digital Recorder, Ela Medical, Paris 2007) was carried out for 48 hours. The rhythm Holter monitorization was repeated for 48 hours in patients, who completed the rehabilitation. The records of the Holter monitorization were uploaded to a computer and analyzed with the Holter software package (ELA Medical SYNESCOPE MultiChannel- Multiday Version 3.10). Initially, the artifacts at the "template" tab, normal and ventricular beats were determined. Then, the average maximum, minimum and mean heart rates were calculated as the mean of the 48-hour recordings. The HRV values were evaluated with the following parameters: Time domain; PNN50 (The division of the NN50 counts to the total NN count), RMSSD (root-mean-square differences of successive NN intervals), ASDNN (mean of the standard deviation in all 5-minute segments), SDNN (standard deviation of all NN intervals). The frequency domain

Table 1. The demographic characteristics, laboratory parameters, lesion and intervention features

	CR Group (n = 68)	Control Group (n = 33)	p value
Age (years)	58.23 ± 9.69	55.48 ± 9.99	0.21
Gender			0.77
Male, n (%)	54 (79.4)	27 (81.8)	
Female, n (%)	14 (20.6)	6 (18.2)	
Diabetes mellitus, n (%)	13 (19.4)	7 (21.9)	0.77
Hypertension, n (%)	24 (35.8)	6 (18.8)	0.08
Hyperlipidemia, n (%)	16 (23.9)	10 (31.3)	0.43
Smoking, n (%)	31 (46.3)	21 (70)	0.03
Previous PCI n (%)	7 (10.4)	4 (12.1)	0.80
LVEF (%)	42.13 ± 11.07	42.12 ± 9.13	0.90
End-diastole diameter (mm)	47.00 ± 3.58	47.06 ± 4.47	0.84
End-systole diameter (mm)	32.03 ± 4.46	32.19 ± 4.97	0.67
Systolic blood pressure (mmHg)	115.80 ± 9.79	111.77 ± 13.81	0.10
Diastolic blood pressure (mmHg)	71.02 ± 7.94	69.03 ± 8.4	0.28
Mean heart rate (beat/min)	66.23 ± 8.04	69.69 ± 10.31	0.069
WBC (×10 ³)	9.61 ± 2.80	9.5 ± 2.34	0.97
Hemoglobin (g/dl)	13.10 ± 1.52	13.79 ± 1.26	0.03
Platelet count (×10 ³)	256.70 ± 83.85	230.41 ± 42.69	0.27
Urea (mg/dl)	15.77 ± 4.51	15.51 ± 5.43	0.49
Creatinine (mg/dl)	0.8 ± 0.17	0.79 ± 0.18	0.55
Total Cholesterol (mg/dl)	179.96 ± 47.41	182.48 ± 41.33	0.51
LDL-C (mg/dl)	120.36 ± 44.61	117.84 ± 35.26	0.70
HDL-C (mg/dl)	35.60 ± 10.54	31.38 ± 8.6	0.08
Triglycerides (mg/dl)	114.95 ± 94.11	167.48 ± 163.46	0.056
Sodium (mEq/L)	140.07 ± 2.57	140.64 ± 2.25	0.19
Potassium (mEq/L)	4.43 ± 0.39	4.27 ± 0.45	0.10
Troponin max (ng/mL)	91.99 ± 97.62	89.34 ± 87.76	0.71
CK-MB max (ng/mL)	180.02 ± 163.67	198.35 ± 140.27	0.27
Time to the start of rehabilitation (days)	62.21 ± 29.33	-	
Drugs			
ASA, n (%)	68 (100)	33 (100)	1.0
Klopidogrel, n (%)	42 (61.8)	17 (51.5)	0.32
Ticagrelor, n (%)	26 (38.2)	16 (48.5)	0.32
Beta-blocker, n (%)	66 (98.5)	33 (100)	0.99
ACE-I, n (%)	60 (89.6)	30 (90.9)	0.83
ARB, n (%)	6 (9.1)	2 (6.1)	0.60
Statin, n (%)	68 (100)	32 (97)	0.99
Nitrate, n (%)	7 (10.6)	2 (6.1)	0.45
Diuretics, n (%)	6 (9.1)	2 (6.1)	0.60
Spironolactone, n (%)	27 (40.9)	9 (27.3)	0.18
Myocardial infarction region			0.66
Anterior, n (%)	34 (50)	15 (45.5)	
Inferior, n (%)	34 (50)	18 (54.5)	
Location of the responsible lesion			0.77
LAD, n (%)	35 (53)	15 (45.5)	
CX, n (%)	12 (18.2)	7 (21.2)	
RCA, n (%)	19 (28.8)	11 (33.3)	
Intervention			0.55
Stent, n (%)	66 (97)	33 (100)	
PTCA, n (%)	2 (3)	-	
Duration of pain (min)	205.56 ± 202.61	142.96 ± 133.36	0.11
Door-to-balloon time (min)	23.46 ± 11.60	22.16 ± 10.72	0.60

Data are shown as mean±standard deviation or number (%). ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers, ASA = acetylsalicylic acid, CKMB = creatinine kinase MB isoenzyme, Cx = circumflex artery, HDL-C = high density lipoprotein cholesterol, LAD = left anterior descending artery, LDL-C = low density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, PCI = percutaneous coronary intervention, PTCA = percutaneous transluminal coronary angioplasty, RCA = right coronary artery, WBC = white blood cell

HRV parameters were determined in 5 different band intervals: HF (0.15-0.4 Hz), VLF (0.0-0.04 Hz), LF (0.04-0.15 Hz), total power (0.0-2.0) and LF/HF ratio. For the evaluation of the relative changes in the frequency field, HF power HFnu=100×HF power/totalpower), normalized LF power (LFnu=100×LF power/total power) and low/high frequency power ratio (LF/HF ratio=LF power/HF power) were calculated. The TO and TS values (HRT parameters) were automatically calculated with the help of the Holter software package (HRT View Version 0.60–0,1 Munich, Germany) and ventricular premature beats, which provided the conformity criteria for the HRT measurement. The values less than 0 % were accepted for the TO and the values more than 2.5 msec/RR were accepted for the TS [8]. Turbulence loss was accepted as the increase in TO and decrease in TS.

Statistical Analysis

SPSS software package (IBM SPSS Statistics Version 22) was used for the statistical analysis. The continuous variables were expressed in mean ± standard deviation; categorical variables were expressed in percentages. The normal distribution characteristics of the continuous variables were checked with the Shapiro-Wilk normality test.

Independent-samples t-test and Mann-Whitney U test were used for the comparison of the parametric data and Chi-square test and the Fisher’s exact test were used for the comparison of the categorical variables. The analysis of the repeated measurements (before and after the rehabilitation) was performed with the Wilcoxon signed-rank test. For all analysis, *p* < 0.05 was considered as statistically significant.

RESULTS

The evaluation of the demographic characteristics and the laboratory analysis of the patients showed that the smoking rate was significantly higher in the control group (*p* = 0.03). The hemoglobin value was also significantly higher in the control group (*p* = 0.03). The biochemical parameters were comparable in both groups. There was no difference between the groups regarding the systolic and diastolic blood pressure and mean heart rate. The use of the medication was also comparable between the groups (Table 1). There was also no difference between the rehabilitation group and the control group in respect of the MI area, treatment strategies and duration of pain (Table 1).

Table 2. 48-hour Holter findings in the rehabilitation and control groups

	CR Group (n = 68)	Control Group (n = 33)	<i>p</i> value
Mean HR (beat/min)	66.23 ± 8.04	69.69 ± 10.31	0.06
Ventricular extrasystole	624.05 ± 1841.97	129.78 ± 252.40	0.35
QT interval (msec)	415.93 ± 32.35	401.93 ± 29.06	0.03
VT			0.055
Yes, n (%)	11 (16.2)	1 (3)	
No, n (%)	57 (83.8)	32 (97)	
SVT			0.26
Yes, n (%)	25 (36.8)	16 (48.5)	
No, n (%)	43 (63.2)	17 (51.5)	

Data are shown as mean±standard deviation or number (%). HR = heart rate, SVT = supraventricular tachycardia, VT = ventricular tachycardia

Table 3. HRV and HRT parameters obtained from the Holter recordings before the rehabilitation

	CR Group (n = 68)	Control Group (n = 33)	p value
HRV frequency domain analysis			
TP (msec ²)	7133.66 ± 12572.95	4037.30 ± 7005.60	0.41
LF (msec ²)	1964.19 ± 4000.70	989.63 ± 2129.09	0.74
LF (nu)	20.99 ± 7.92	21.20 ± 6.46	0.58
HF (msec ²)	1734.29 ± 4235.26	874.27 ± 3252.12	0.92
HF (nu)	12.19 ± 11.66	11.84 ± 9.71	0.55
LF/HF ratio	2.94 ± 2.12	2.67 ± 1.68	0.67
HRV time domain analysis			
SDNN (msec)	103.74 ± 35.08	99.76 ± 33.33	0.77
ASDNN (msec)	71.80 ± 51.89	58.88 ± 39.15	0.45
RMSSD (msec)	70.81 ± 87.68	52.82 ± 67.10	0.72
pNN50 (%)	9.22 ± 10.85	8.62 ± 8.77	0.85
HRT parameters			
TO	-0.0089 ± 0.027	-0.0027 ± 0.031	0.24
TS	9.26 ± 8.13	7.30 ± 9.16	0.17

Data are shown as mean±standard deviation. CR = cardiac rehabilitation, HR = heart rate, HRV = heart rate variability, HRT = heart rate turbulence, TO = turbulence onset, TS = turbulence slope

There was no significant difference between the groups considering the main findings of the 48-hour Holter monitorization. There was no significant difference between the groups regarding the ventricular extrasystole count, the presence of the supraventricular and ventricular tachycardia. The QT-interval was 415 ± 32 msec and 401 ± 29 msec in the rehabilitation and control groups respectively. The QT-interval was significantly longer in the rehabilitation group ($p = 0.03$) (Table 2).

There was no difference between the pre-rehabilitation frequency domain analysis of the basal HRV parameters (TP, LF, LFnu, HF, HFnu, LF /HF) and time domain parameters (SDNN, ASDNN, RMSSD, pNN50). HRT parameters (TO and TS) were comparable in both groups (Table 3). In the rehabilitation group, there was no significant

difference between HRV and HRT parameters before and after the rehabilitation (Table 4).

The analysis of the subgroup consisting of the patients with a left ventricle ejection fraction below than 40% showed that there was no significant difference between the HRV parameters before and after the rehabilitation. Regarding the HRT parameters; there was no significant difference before and after the rehabilitation for TS, but TO parameter significantly improve with CR (before the rehabilitation: -0.00014 ± 0.021 , after the rehabilitation: -0.0051 ± 0.029 , $p = 0.04$). (Table 5) (Fig. 1).

DISCUSSION

In our study, we found that the 8-week CR program, which STEMI patients underwent at least

Table 4. HRV and HRT parameters in the rehabilitation group before and after the rehabilitation

	Before Rehabilitation (n = 68)	After Rehabilitation (n = 68)	p value
HR (bpm)	66.3 ± 8.09	66.9 ± 7.50	0.52
HRV frequency domain analysis			
TP (msec ²)	7133.6 ± 1257.8	5183.0 ± 1220.8	0.88
LF (msec ²)	1964.1 ± 400.0	1376.4 ± 411.7	0.84
LF (nu)	20.9 ± 21.7	21.7 ± 8.0	0.28
HF (msec ²)	1734.2 ± 423.5	1139.0 ± 511.4	0.82
HF (nu)	12.1 ± 11.6	11.0 ± 9.4	0.87
LF/HF ratio	2.9 ± 2.1	3.2 ± 2.4	0.51
HRV time domain analysis			
SDNN (msec)	103.7 ± 35.0	102.7 ± 28.1	0.69
ASDNN (msec)	71.8 ± 51.8	63.5 ± 28.9	0.95
RMSSD (msec)	70.8 ± 8.7	52.9 ± 5.6	0.63
pNN50 (%)	9.2 ± 8.1	8.0 ± 7.2	0.96
HRT parameters			
TO (%)	-0.0089 ± 0.002	-0.0077 ± 0.002	0.72
TS (msec/RR)	9.6 ± 8.3	7.3 ± 6.4	0.26

Data are shown as mean±standard deviation. CR = cardiac rehabilitation, HR = heart rate, HRV = heart rate variability, HRT = heart rate turbulence, TO = turbulence onset, TS = turbulence slope

one month after PCI, had no significant effect on the HRV and HRT parameters. The subgroup analysis showed that CR did not provide any significant change in HRV and HRT parameters in patients, who had a normal or mildly affected LVEF (LVEF > 40%). On the other hand, we determined a significantly positive effect in TO for patients with an LVEF lower than 40%. Our study is the first study in the literature, which is focused on the HRT parameters before and after CR in post-STEMI patients.

Most of the meta-analyses, which focused on the effects of CR on the cardiac mortality in acute MI patients, were conducted before the introduction of the modern revascularization techniques like the thrombolytic treatment and primary PCI. Hereby, it

might come to mind whether the effects of CR on the mortality were still in place after the introduction of the modern revascularization techniques. Although, it was shown in a few studies that mortality was decreased, the lack of randomized and controlled studies focused on this topic should be taken into consideration. Goel *et al.* [9] has evaluated a retrospective study (published 2011) focused on a large patient population (n = 2395), who underwent PCI between 1994 and 2008. In conclusion, it was determined that CR decreased significantly all-cause and cardiac mortalities after PCI [9]. In a meta-analysis, which was conducted with the support of the Cochrane Collaboration and published in 2001 and revised in 2005, 51 studies comprising 8440 patients

Table 5. HRV and HRT findings in patients with LVEF < 40 % before and after the rehabilitation

	Before Rehabilitation (n = 24)	After Rehabilitation (n = 24)	p value
HRV frequency domain analysis			
HR (bpm)	67.62 ± 9.05	68.42 ± 7.58	0.83
TP (msec ²)	8628.11 ± 15424.91	7926.88 ± 18159.08	0.71
LF (msec ²)	2436.55 ± 4759.98	2314.64 ± 6051.47	0.87
LF (nu)	22.57 ± 8.38	23.52 ± 8.62	0.67
HF (msec ²)	2337.55 ± 5007.81	2478.55 ± 7741.08	0.82
HF (nu)	15.30 ± 12.24	15.76 ± 11.95	0.50
LF/HF ratio	2.39 ± 1.54	2.31 ± 1.54	0.91
HRV time domain analysis			
SDNN (msec)	104.78 ± 35.33	98.42 ± 32.18	0.12
ASDNN (msec)	82.95 ± 60.70	72.10 ± 42.74	0.97
RMSSD (msec)	48.64 ± 42.29	58.00 ± 39.40	0.11
pNN50 (%)	9.84 ± 13.08	8.53 ± 6.63	0.95
HRT parameters			
TO (%)	-0.00014 ± 0.021	-0.0051 ± 0.029	0.04
TS (msec/RR)	6.12 ± 5.18	5.08 ± 5.08	0.50

Data are shown as mean±standard deviation. CR = cardiac rehabilitation, HR = heart rate, HRV = heart rate variability, HRT = heart rate turbulence, TO = turbulence onset, TS = turbulence slope

were systematically investigated [2]. In patients, who underwent cardiac rehabilitation, all-cause and cardiac mortalities decreased 27 % and 31 % respectively. There was also a 19 % decrease in combined events (non-fatal MI, CABS, PTCA) [2].

The cardiac autonomous functions are impaired in MI patients and this impairment is correlated with the mortality and morbidity. Kleiger *et al.* [10] investigated HRV parameters with 24-hour Holter monitorization after 11 ± 3 days from the acute event in 808 patients. They determined a 2.4-fold increase in the all-cause mortality during the 31-month follow-up in the group with SDNN > 50 msec compared to the SDNN < 50 msec [10].

In a randomized and controlled study conducted

by Oliveira *et al.* [11] and published in 2014, the effects of 8-week exercise-based CR on the cardiac autonomous functions were investigated in the MI patients. The HRV parameters were measured after this exercise program and no difference was detected between the exercise and control group regarding the HRV parameters. Only the VO₂ peak level was significantly increased in the exercise group [11]. As the LVEF level was > 50% in this study, we assumed that the PCI implementation was efficient. This study was conducted a short time ago when the revascularization techniques and pharmacological agents were widely used and its results are consistent with our study.

The data related to the MI patients, who

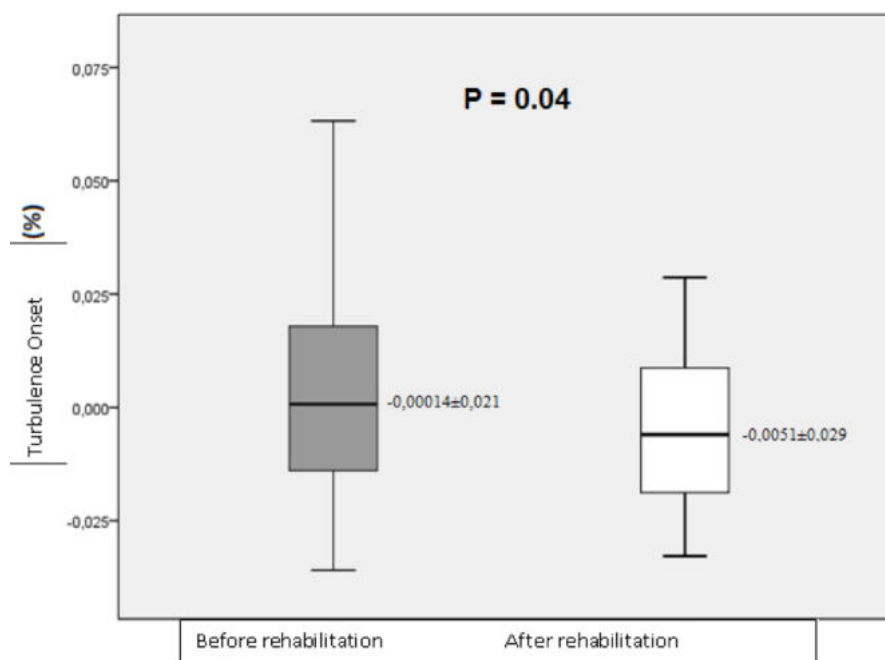


Fig. 1. Turbulence onset value in patients with LVEF < 40% before and after the rehabilitation.

underwent CR, were based on the studies conducted 30 years ago. At that time, efficient revascularization techniques were not introduced yet and the use of several anti-platelet and anti-ischemic agents and the statin derivatives was not prevalent. Therefore, the cardiac damage was more severe and the survival rate was relatively lower. This fact brought along the questioning of the benefits of CR, which was effective at that time. In other words, the faster the treatment and the better the revascularization, the milder is the cardiac damage and consequently the benefit of CR is not much different from its benefit in the healthy population. In our study, our findings – no significant difference between the pre- and post-rehabilitation HRV and HRT values in the control group – confirm these results.

In our study, all patients were diagnosed with STEMI and underwent PCI. Other patients with acute coronary syndrome (ACS) were excluded from the study. Therefore, we can suggest that the study group was balanced and homogeneous. Studies related to the exercise program contained certain differences. In our study, we implemented an 8-week exercise program, which consisted of approx. 30-minute 4 sessions per week. The targeted heart rate was 70-85 % of the resting heart rate. We did not detect any difference between the rehabilitation and control group regarding

the HRV parameters. There was also no difference between the HRV parameters before and after the rehabilitation. These findings might be related to the revascularization at the early stage, minimally valve damage and drug treatment. Probably, the short door-to-balloon time and high rate of the compliance to the drug treatment prevented the deterioration of the cardiac autonomous functions and improved the impaired functions at the early stage. It is well known that post-MI acute sudden death rate is particularly high in the first month. In our study, the rehabilitation was started at least one month after the acute MI (mean time: 62 ± 29 days). Prior to the rehabilitation program, Holter monitorization was carried out for the evaluation of the baseline HRV and HRT parameters. Regarding the control group, 48-hour rhythm Holter monitorization was performed at least one month after the acute MI (mean: 86 ± 57 days). In our study, as it was mostly within the normal limits in both groups and there was no significant difference between the groups regarding the HRV and HRT parameters, we believe that these may be related to the study design, in which the measurements were not done in the first month, which is period with the highest level of the risks of ACD and the cardiac autonomous dysfunction.

The relatively limited cardiac damage may decrease the efficacy of the exercise-based CR and

consequently, no difference in HRV and HRT parameters was detected after CR. The baseline values of the HRV parameters were higher in our study compared to other studies and were mostly within normal limits. These findings might be explained by the early and effective revascularization and the following preservation of the cardiac autonomous functions and with the normal HRV and HRT parameters comparable to the normal population. In addition, like the abovementioned study, the compliance to the treatment, use of the beta-blockers and ACE-inhibitors [12, 13], which particularly improve the cardiac autonomous functions, during the study and high tolerance of the drugs, might be related to this finding.

One of the subgroup analyses in the study ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) showed that the patency of the artery responsible for the MI, was the major determinant in the post-MI baroreceptor response in the patient population, who underwent coronary angiography [14]. The post-MI baroreceptor activity and cardiac autonomous functions declined acutely. Nevertheless, it was demonstrated that the HRT parameters, which were one of the indicators of the cardiac autonomous functions, improved after the reperfusion [15]. This may be explained by the limited impact on the autonomous functions and faster improvement of them along with the corresponding HRT parameters as a result of the revascularization at the early stage with modern techniques. According to the findings of our study, CR was carried out on patients, who had mildly affected HRV and HRT parameters with levels similar to the normal population. This may be the reason that the post-rehabilitation levels of these parameters did not change compared to the pre-rehabilitation levels.

HRT is usually abnormal in patients with heart failure. It was determined that TS below 2.5 m/sec was related to the risk of the cardiac complications in patients with heart failure (EF < 35 %) [16]. In our study, in the subgroup analyses, we detected a significant difference between the TO values before and after the rehabilitation in patients with an LVEF below 40%.

Therefore, it may be suggested that the patients, who had delayed revascularization and treatment and consequently increased cardiac damage followed by

decreased SVEF, had a distinct clinical condition. It may be also suggested that CR is more effective in decreasing the mortality in patients with an LVEF lower than 40%. However, further studies are needed for the confirmation.

Limitations

One of the limitations of our study is the lack of the 48-hour rhythm Holter monitorization in both rehabilitation and control groups within the same time. This may have caused some heterogeneity in HRV and HRT values. The HRV and HRT parameters were obtained from the rhythm Holter recordings during the routine daily activities. The evaluation of the Holter recordings during the exercise may present different results.

CONCLUSION

We did not determine any significant difference between the HRV and HRT parameters before and after the rehabilitation, in patients with STEMI who was treated with primary PCI. However, there was a significant and positive difference in TO parameter in patients with a left ventricular ejection fraction less than 40%.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Evaluation of the effects of laparoscopic adjustable gastric banding versus laparoscopic sleeve gastrectomy on weight loss

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ABSTRACT

Objectives: Obesity has become one of the most serious and ever increasing health problems of our times. Diet, exercise and medical treatment have proven to be insufficient. Operations such as laparoscopic adjustable gastric banding (LAGB) and laparoscopic sleeve gastrectomy (LSG) have gained popularity. The purpose of this study is to conduct a retrospective comparative analysis of the clinical results gained from patients treated with LSG and LAGB due to morbid obesity.

Methods: The patients included in the study were selected among those who were diagnosed with morbid obesity and were operated with LAGB (n = 55) and LSG (n = 52) from May 2007 to December 2012. Both groups were compared in terms of the demographic characteristics, preoperative and postoperative conditions.

Results: The groups were similar in terms of age, sex and BMI. In the 6th month, there was a notable loss of appetite in the LSG group patients compared to the LAGB patients (69.2% vs. 23.6%, $p < 0.001$). The rate of excess weight loss in the LAGB group was $23.93\% \pm 7.98\%$ and $31.7\% \pm 7.49\%$ in the LSG group in the postoperative 6th months ($p = 0.002$). The rate of excess weight loss was $45.36\% \pm 10.92\%$ in the LAGB group and $60.3\% \pm 9.81\%$ in the LSG group in the postoperative 12th months ($p < 0.001$).

Conclusions: When the two surgical operations for morbid obesity are compared LSG is found to be a more successful method in terms of body weight loss. Nevertheless, longer hospitalization can be associated with the technically more complicated nature of the operation and the fact that it requires resection.

Keywords: Obesity, bariatric surgery, sleeve gastrectomy, laparoscopic adjustable gastric banding

Obesity is a serious epidemic problem with increased clinical significance worldwide as it is associated with several comorbidities and account for more than 2.5 million deaths per year worldwide [1-3]. Although numerous nonsurgical options are available to treat obesity, surgical interventions have

proven to be the most reliable and effective methods for achieving weight loss [4]. Laparoscopic adjustable gastric band (LAGB) and laparoscopic gastric bypass (LGB) are the most frequently performed surgical interventions. However, the long-term outcomes of gastric banding procedures are often unsatisfactory [5].

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Laparoscopic sleeve gastrectomy (LSG) is a modification of the Magenstrasse and Mill procedure, and has been proposed as an alternative restrictive bariatric procedure to the most popular LAGB [5]. The purpose of this prospective clinical trial was to measure and compare perioperative clinical and weight-loss outcomes between LSG and LAGB for the treatment of obesity.

METHODS

Study Design

This study was approved by the Scientific Research Evaluation Committee at Ankara Numune Training and Research Hospital. Morbidly obese patients who underwent LAGB or LSG between May 2007 and December 2012 at Ankara Numune Training and Research Hospital were enrolled in the study. Patients who underwent other surgical techniques to treat morbid obesity or re-do surgery were excluded from the study. The decision to undergo surgery in individual patients was based on the National Heart Lung and Blood Institute criteria, which stipulate the necessity of surgical intervention. Patients were interviewed before surgery, the expectations of the patients and physicians were recorded and a joint decision was taken regarding the surgical technique to be used. The patients were assessed by a dietician and received dietary guidance tailored to their individual characteristics to help maintain their target weight loss before surgery. In the pre-surgical period, respiratory exercise and prophylactic anti-thromboembolic drugs were started to minimize lung disorders or thromboembolism. The medical history of each patient was carefully reviewed before the procedure, and a physical examination was performed. After completing blood tests and radiological imaging in the pre-surgical period, the subjects underwent routine consultations in internal medicine, thoracic disease, endocrinology, dietetic, and psychiatric units as part of the multidisciplinary approach. Patients were given anti-thromboembolic prophylaxis before and after surgery till they discharged.

Patients in the LAGB group returned to the clinic every month for any necessary manipulation of their bands. Weight loss and body mass index (BMI) were

regularly measured at each outpatient visit. Patients in the LAGB and LSG group were scheduled at 6 and 12 months after surgery to assess medical history, measure height and weight, and conduct basic biochemical tests. At the 6th-month visit, patients were also asked about any changes in appetite. The loss of excess weight was measured as a percentage of the patient's ideal weight determined before surgery. Excess weight was taken as the weight in kilograms above the weight at a BMI of 25 kg/m².

Interventions

All surgical procedures were performed by one of the authors (MMO) as primary surgeon at Ankara Numune Training and Research Hospital.

LSG

was performed using a four-ports approach. The gastrocolic ligament was divided by a vessel sealer device (LigaSure Vessel Sealing System™; Valleylab, Boulder, CO, USA). The greater curvature of the stomach and the fundus were mobilized. Sleeve gastrectomy was performed by multiple applications of a 60 mm stapler (Echelon 60 Endopath Stapler and Cutter; Ethicon Endo-Surgery, Cincinnati, OH, USA or EndoGIA 60 mm, Covidien, NewHaven, CT, USA) with staple-line reinforcement (Seamguard, Bioabsorbable Staple Line Reinforcement; W.L. Gore and Associates Inc. Flagstaff, AZ, USA), which extended 4-6 cm from the pylorus toward the angle of His. Intraoperative gastroscopy was performed to evaluate the integrity of the staple line and to perform an air-leak test. The resected stomach was removed through an extended trocar located at the left upper quadrant.

LAGB

LAGB was performed with four abdominal ports. A retro-gastric window was bluntly created using the pars flaccida technique. An adjustable gastric band (Soft Gastric Band Premium; A.M.I. GmbH, Feldkirch, Vorarlberg, Austria) was primed on the back table with approximately 3 mL of saline solution. The band was then inserted into the abdomen, placed below the gastroesophageal junction creating a small pouch and buckled in place. Three anterior non-absorbable interrupted gastro-gastric stitches were

placed to secure the band in place. The band tubing was connected to the access port, which was implanted subcutaneously and secured to the rectus abdominis fascia with interrupted, non-absorbable sutures.

Statistical Analysis

Data are expressed as the mean \pm standard deviation. The proportions of males/females were compared between the two groups using Pearson's χ^2 test. The percent of excess weight lost at 6 and 12 months was compared using the Mann-Whitney U test. Other continuous variables were compared using Student's t test. Results with p-value of ≤ 0.05 were considered statistically significant. Correlation analyses were performed using Pearson's correlation test. All analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 107 matched patients were included in the study, of which 55 underwent LAGB and 52 underwent LSG. There were 83 (77.6%) females and 24 (22.4%) males. The mean age of the patients was 35.83 years (range; 19-61). The mean body weight, BMI, and ideal body weight before surgery were 127.62 (91-200) kg, 46.4 (34.2-64.1) kg/m², and 61.7 (43.2-89.8) kg, respectively.

Table 1 compares the clinical characteristics, including proportions of patients with comorbidities, between the groups of patients. Of 55 patients who underwent LAGB, 40 (72.7%) were females and 15 (27.2%) were males. Their mean age was 36 (19-60) years. The mean body weight, BMI, and ideal body weight were 126.1 kg (91-174), 44.96 \pm 6.6 kg/m², and 61.2 \pm 12.1 kg. Comorbidities included diabetes

Table 1. Comparison the clinical characteristics, including proportions of patients with comorbidities in both groups

	LAGB (n = 55)	LSG (n = 52)	p value
Sex (F/M)	40/15	43/9	0.812
Age (years)	39 (19-60)	37 (20-61)	0.594
Weight (kg)	126.1 (91-174)	134.6 (105-200)	0.182
BMI (kg/m ²)	44.96 \pm 6.6	51.32 \pm 3.2	0.720
Ideal weight (kg)	61.2 \pm 12.1	61.23 \pm 4.6	0.910
Comorbidities			
DM	11 (20%)	4 (7.7%)	
HT	11 (20%)	3 (5.8%)	
OSAS	4 (7.2%)	-	
Gallbladder stones	3 (5.4%)	1 (1.9%)	
Coronary diseases	1 (1.8%)	-	
OA	1 (1.8%)	-	

LAGB = Laparoscopic adjustable gastric banding, BMI = Body mass index, LSG = Laparoscopic sleeve gastrectomy, DM = Diabetes Mellitus, HT = Hypertension, OSAS = Obstructive sleep apnea syndrome, OA = Oral antidiabetic, F = Female, M = Male

mellitus in 11 (20%) patients, hypertension in 11 (20%) patients, obstructive sleep apnea syndrome in 4 (7.2%) patients, gallbladder stones in 3 (5.4%) patients, coronary artery disease in 1 (1.8%) patient, osteoarthritis in 1 (1.8%) patient, and gallbladder polyp in 1 (1.8%) patient.

Of 52 patients who underwent LSG, 43 (82.7%) were females and 9 (17.3%) were males. Their mean age was 37 (20-61) years. The mean body weight, BMI, and ideal body weight before surgery were 134.6 (105-200) kg, 51.32 ± 3.2 kg/m², and 61.23 ± 4.6 kg. Comorbidities in this group included diabetes mellitus in 4 (7.7%) patients, hypertension in 3 (5.8%) patients, and gallbladder stones in 1 (1.9%) patient.

Statistical analyses revealed that age ($p = 0.594$), sex distribution ($p = 0.812$), ideal weight ($p = 0.91$) and pre-surgical body weight ($p = 0.182$) were not significantly different between the two groups. Although body mass was greater in the LSG group than in the LAGB group, this difference was not statistically significant ($p = 0.72$).

All procedures in both groups were completed laparoscopically and there were no intraoperatively surgical complications. All four patients whose gallbladder stones were detected before surgery underwent laparoscopic cholecystectomy in the same session. No deaths were reported in either of the groups over the 1-year follow up. The mean hospital stay was 2.8 days (1-25) in the LAGB group and 6.2 days (4-11) in the LSG group. The mean hospital stay was therefore significantly longer in the LSG group than in the LAGB group ($p < 0.001$). One patient in the LAGB group developed acute necrotizing pancreatitis five days after surgery. The patient was discharged with appropriate monitoring and treatment. Other complications in the LAGB group included atelectasia, port infection, and intraabdominal infection, which occurred in three, two, and one patient, respectively. Therefore, the early morbidity rate in the LAGB group was 12.7%. In the LSG group, atelectasia, wound site infection, and hemorrhage from the staple line occurred in three, one, and one patients,

Table 2. Comparison the changes in the study outcomes between the two groups

	LAGB	LSG	<i>p</i> value
Weight Loss in 6 th month (kg)	15 ± 5.19	24.79 ± 8.91	0.001
EWL in 6 th month (%)	23.93 ± 7.98	31.7 ± 7.49	0.002
Loss of Appetite in 6 th month	13 (23.6%)	36 (69.2%)	< 0.001
Weight Loss in 12 th month (kg)	28.5 ± 10.92	41 ± 14.44 kg	< 0.001
EWL in 12 th month (%)	45.36 ± 10.92	60.3% ± 9.81 %	< 0.001
Length of stay (days)	2.8 (1-25) day	6.2 (4-11) day	< 0.001
Early Complications	7 (12.7%)	5 (9.6%)	0.139
Pancreatitis	1	-	
Atelectesia	3	3	
Port infection	2	-	
Abdominal infection	1	-	
Hemorrhagia	-	1	
Wound site infection	-	1	

LAGB = Laparoscopic adjustable gastric banding, EWL = Excess weight loss, LSG = Laparoscopic sleeve gastrectomy

respectively. The patient with hemorrhage was treated conservatively. The early morbidity rate in the LSG group was 9.6%. Although the early morbidity rate was higher in the LAGB group than in the LSG group, the difference between the two groups was not statistically significant ($p = 0.139$).

In the long term, adjustable gastric band was removed from 11 (20%) patients. The reason for band removal was band intolerance (intractable vomiting, pain, and inability to comply with diet) in 3 (27.2%) patients, insufficient weight loss in 4 (36.4%) patients, and band complications (slippage, erosion, leak or disconnection) in four (36.4%) patients.

Table 2 compares the changes in the study outcomes between the two groups of patients. The mean weight loss at 6 months after surgery was 15 ± 5.19 kg and 24.79 ± 8.91 kg in the LAGB and LSG groups, respectively. The percent of excess weight lost at 6 months after surgery was $23.93\% \pm 7.98\%$ and $31.7\% \pm 7.49\%$ in the LAGB and LSG groups, respectively. The mean weight loss ($P = 0.001$) and the percent of excess weight lost ($p = 0.002$) at 6 months were both significantly greater in the LSG group than in the LAGB group. Overall, 13 (23.6%) patients in the LAGB group and 36 (69.2%) patients in the LSG group reported a decrease in appetite at 6 months after surgery. The proportion of patients who reported a decrease in appetite was significantly greater in the LSG group than in the LAGB group ($p < 0.001$).

At 12 months after surgery, the mean weight loss was 28.5 ± 10.92 kg and 41 ± 14.44 kg in the LAGB and LSG groups, respectively. The percent of excess weight lost was $45.36\% \pm 10.92\%$ and $60.3\% \pm 9.81\%$ in the LAGB and LSG groups, respectively. The mean weight loss ($p < 0.001$) and percent loss of excess weight ($p < 0.001$) were significantly greater in the LSG group than in the LABG group (see Table 2).

DISCUSSION

LAGB is increasingly being performed because of its relatively low complexity and adjustability, as well as its low perioperative morbidity (1%-5%) and mortality (0%-0.05%) rates [6, 7]. Furthermore, the procedure is considered reversible as the stomach regains its normal anatomy after removing the band

[8]. However, there are some limitations to LAGB. In particular, band-related complications such as esophageal dilatation, food intolerance, gastric necrosis, band slippage, band dilation, and pouch dilation occur in 15%-58% of patients undergoing LAGB [8-10]. Furthermore, many patients experience inadequate weight loss or weight regain after an initial period of weight loss. Inadequate weight loss and weight regain were indications for repeated surgery in 27%-100% of patients who underwent LAGB [11]. LSG was initially introduced as the first step of the duodenal switch procedure but it is increasingly being offered as a primary independent bariatric operation [12].

In the present study, the percent of excess weight lost at 12 months after surgery was 60.3% for LSG and 45.36% for LAGB. Our data are consistent with the results of prospective randomized clinical trials by Himpens *et al.* [13] and Varela [5] that compared gastric banding with sleeve gastrectomy. In both trials, sleeve gastrectomy was associated with superior weight loss but with a greater number of complications compared with gastric banding. Likewise, in a meta-analysis that included 940 patients, Shi *et al.* [1] reported that the percent of excess weight lost at 1 year was 59.8% for LSG and 37.8% for LABG. According to these prior reports, LSG is effective in the short term and may offer some advantages over existing options, namely LAGB and laparoscopic Roux-en-Y gastric banding [1]. Based on these prior reports and our present findings, we consider that LSG is more effective than LAGB for achieving weight loss.

There is substantial evidence showing that gastric restriction is the main mechanism for weight loss after LAGB [14]. LSG was originally thought to be a purely mechanically restrictive procedure [15]. However, there is evidence that other factors might contribute to weight loss after LSG. In particular, LSG seems to increase gastric emptying [16, 17]. The levels of ghrelin, an orexigenic peptide that stimulates appetite, were reported to decline, causing early satiety [18]. In a systematic review, Anderson *et al.* [19] reported that LSG has significant effects on ghrelin levels at 3, 6, and 12 months, leading to considerable reductions in its circulating levels after LSG procedure. In our study, a significantly greater proportion of patients in the LSG group reported a reduced appetite at 6 months after surgery compared with patients in the LAGB

group. This finding, although we didn't measure ghrelin levels, may be due to a reduction in ghrelin levels in LSG group.

Although LAGB is an appealing bariatric procedure because of it has minimal mortality and almost negligible perioperative complication rates [20-22], and also it is reversible, allowing a "return to normal" in cases of intolerance [23, 24], unfortunately, LAGB is fraught with a high rate of long-term complications, leading to a large subset of patients who require reoperations, replacements, reconstructions, and explanations for various reasons [9, 20, 25]. Mittermair *et al.* [26] have shown that 50.4% complications occurred in their series. Tolonen *et al.* [20] have shown that major late complications (including band erosions, slippage, leakage leading to major reoperation) occurred in 24.4% of patients. Also Khan *et al.* [27] have emphasized that LAGB is associated with a cumulative failure and complication rate of up to 30%. In our study the band was removed from 11 (20%) patients.

In a review of randomized controlled trials, Chakravarty *et al.* [28] reported that LAGB is associated with shorter length of hospital stay than other bariatric procedures. Likewise, Shi *et al.* [1] reported that the mean hospital stay was 4.4 days for LSG and 1.7 days for LAGB. Similarly, the length of hospital stay was significantly shorter in the LAGB group than in the LSG group in our study. However, this is not surprising considering that LSG is a more complicated procedure than LAGB.

CONCLUSION

Follow-up in our study is comparably shorter than other studies. Therefore complications related to the band and the rate of band removal might be higher than we found with a longer follow up. Also, rate of the excess weight loss might be lower in LSG group with longer follow up. However, with the current data we conclude that LSG was more successful in terms of the magnitude of weight loss after surgery and the loss of appetite.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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Determination of factors affecting the quality of life in children with asthma

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ABSTRACT

Objectives: This study has been conducted in order to determine the factors affecting the quality of life in children with asthma.

Methods: The study sample consisted of 103 children (aged 7-16). Data has been collected using socio-demographic questionnaire and Pediatric Asthma Quality of Life Questionnaire (PAQLQ) through face to face interviews.

Results: Seventy-eight point six percent of the children's daily activities were affected due to asthma. Evaluating the sub-groups mean scores of the life quality of the children; the highest mean score was in the symptoms group. The activity limitation sub-group mean score was significantly decreased with the increase of the number of people living in the house and other siblings having asthma too. The symptom sub-groups mean scores of the children that are exposed to smoke and psychological factors and which state that their daily activities are being affected was lower. The emotional function sub-groups mean score of the children that are exposed to psychological factors was significantly decreased. The scale total mean score of the children with sensitivity to cockroach and psychological factor stimulant was lower ($p < 0.05$).

Conclusions: It's been suggested that the stimulants which trigger the symptoms, asthma disease, accurate and effective medication treatment and self-care should be taught to the child and the family; home care continuity should be ensured and arranging the environment to reduce the child's connection with the allergens that could trigger the asthma attack is necessary.

Keywords: Asthma, children, quality of life, risk factors, nursing

Asthma, which is thought to affect about 300 million people worldwide, is an increasingly common disease with increasing morbidity in all age groups. It is one of the most common chronic diseases in childhood. Global rate of asthma is 1-18% according to the Global Initiative for Asthma (GINA) 2016 report [1]. It is estimated that approximately 250000 people die annually due to asthma. This figure is expected to reach 400 million people by 2025.

Asthma is a multifactorial disease. Environmental factors (allergens, smoking, infections, air pollution) and personal factors (genetics, sex, obesity) play a role in the emergence of this disease together. Genetic factors are the most influential factors for the development of asthma. The factors that lead to asthma exacerbations are generally environmental factors. The effects of genetic and environmental risk factors are chronic inflammation of the airways. Structural

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changes, bronchial hyperactivity, and symptoms appears after airway obstruction along with inflammation [1, 2].

Individuals with chronic illness have difficulties in carrying out their daily and self-care activities. In addition, they may have to go to the hospital repeatedly, suffer from side effects of the medications or live dependent to a medical device. These conditions impair the physical and psychological well-being of the chronically ill individuals. The children and adolescents with chronic illness have lower rates of performing of daily activities and physical activities compared to healthy children [3]. The results of the studies on the subject show that asthma affects children's daily lives, limits their activities and has negative effects on their feelings [4].

The children with asthma may sometimes experience feelings as guilt, loneliness, fear, anxiety and disappointment. Their school life, daily life and especially sports activities may be interrupted by the disease [5]. The most important clinical signs of asthma are shortness of breath, coughing, wheezing, being affected by cigarette smoke or other environmental irritants, weather changes, attacks of viral infections, sleep disturbances and adverse effects of treatment applications, are the most important factors which affect the quality of life of asthmatic children [6]. It is stated that asthma patients are at high risk of respiratory illnesses in three months of the year (January, May, September) due to allergenic substances (domestic and outdoor) and environmental pollutants such as ozone and carbon monoxide. Increased air pollution in winter, more respiratory tract infections, increased pollen levels in the spring cause an increase in asthma symptoms. The daily life of children with asthma is negatively affected by the signs of coughing and shortness of breath due to these causes. In addition, the participation of children with asthma in sporting activities is often prevented by their parents and they are not allowed to participate in school physical education classes to run, to run and play. School absences occur especially in the winter months because of the exacerbation of symptoms. It has also been reported that school failure due to illness and school failure in asthmatic children as a result of occasional need to go to the hospital. It is necessary that children with asthma are approached holistically during the treatment phase and the quality of life must be evaluated

and considered when these factors are taken into account [7].

Nowadays, the increase in the desire for healthy life, the increase in lifespan because of the developments in every fields, especially in the health field have caused the expectation of continuing a quality life in chronic diseases [8, 9]. It is known that adult individuals with low quality of life experienced more life quality problems in their childhood and focus on quality of life at early ages declines the quality of life problems in adulthood [10]. Therefore, it is important to strengthen the child by early identification of the problems that may negatively affect the quality of life of children with chronic diseases. Asthma management prevent the development of the symptoms of asthma help asthmatic children and their families to maintain their daily life activities in good quality [9, 11]. For a quality of life, children with asthma and their parents are taught with the cause of asthma, the stimulants that initiate the disease, the prevention of acute attacks, asthma symptoms and treatment, care principles and follow-ups, thus they can manage their disease.

METHODS

This descriptive study was conducted between March 28 and May 28, 2016 at Pendik Training and Research Hospital-Pediatric Chest Diseases Polyclinic and Child Allergy-Immunology Polyclinic of Marmara University (Istanbul/Turkey).

Participants

The sample consisted of the children who applied to the polyclinic and who were followed up for asthma. Selection criteria for the sample: in the 7-17 age group, at least 3 months since the diagnosis of asthma [12], no communication barriers of the children and their parents, and no other chronic disease. In total, 467 children with asthma who applied to the outpatient clinic between March 28 and May 28, 2016 in accordance with the selected sample selection criteria were included. In this study, a purposive sample was addressed, the data were collected on different days of the week. Patients who did not meet the sampling selection criteria were excluded from the study and 103 children from 467 asthmatic children who were

reached were included in the sample.

Ethical Considerations

Written permission from the hospital and ethical consent from the ethics committee were obtained prior to the conduct of this study. The childrens' parents were informed of the aim and protocol of this study and both their written and oral consent were obtained. In the study, the related ethical principles of the Informed Consent Policy, Volunteer Policy, and Privacy Protection Policy were fulfilled.

Data Collection

Data has been collected using socio-demographic questionnaire and Pediatric Asthma Quality of Life Questionnaire (PAQLQ) through face to face interviews. The sociodemographic questionnaire form consists of 37 questions prepared by the researcher based on the relevant literature. In the sociodemographic questionnaire, the questions for the parameters such as the age of the child, gender, parents' ages, educational status, income level, as well as questions about the severity of asthma, the time after asthma diagnosis, and the number of hospitalizations which were considered to affect quality of life were included.

Pediatric Asthma Quality of Life Questionnaire (PAQLQ): The scale is a disease and age-specific quality of life scale, was developed by Juniper *et al.* [13] in 1996 to measure the physical, mental and social disorders of asthmatic children in the 7-17 age group. The general internal consistency coefficient of the scale was 0.85, the emotional function score was 0.80, the activity restriction score was 0.84. The scale consists of 23 questions collected under three areas:

1. Field: Emotional function score (5, 7, 9, 11, 13, 15, 17, 21. questions)
2. Field: Activity limitation score (1, 2, 3, 19. ve 22. questions)
3. Field: Symptoms score (4, 6, 8, 10, 12, 14, 16, 18, 20, 23. questions)

Every question on the scale was equally weighted. The results were described as "average score per question" for both total quality of life and each field. Thus, four points including three field scores and total scale points are obtained [14]. Both the total quality of life score and the field scores of the scale vary between 1 and 7. Thus, the results of both the five-

question area and the ten-question area were described as a score in the range of 1 to 7. In the field of emotional function, minimum score was 8 and maximum score was 56 while the minimum point was 5 and maximum point was 35 in the field of activity restriction. The minimum score was 10 and maximum was 70 in the field of symptoms when the minimum total life quality score was 23 and maximum total life quality score was 161. The total quality of life score was calculated from the mean score of all the questions. The highness of mean scores indicated that the quality of life was good.

The Turkish validity and reliability study of the Quality of Life Scale of Asthmatic Children was conducted by Yüksel *et al.* [14] in 2019. The Cronbach Alpha values of 122 children with asthma were 0.86 for emotional function field, 0.80 for activity restriction field and 0.90 for symptoms field [14]. In this study, Cronbach Alpha values were 0.82 for emotional function, 0.60 for activity restriction, 0.86 for symptoms and 0.90 for total score.

Statistical Analysis

The data were statistically analysed with SPSS 21.0 (Statistical Package for Social Sciences) program. Number, percentage, correlation, importance test of the difference between two means in two-some groups, Mann-Whitney U test, Kruskal-Wallis analysis for groups with 3 or more, and in the case that the p value results less than 0.05 in the analysis of multi-groups; in order to determine the group which creates the difference, the Post-Hoc tests such as Independent Samples t test with Bonferroni correction and Mann-Whitney U test with Bonferroni correction were used to evaluate the data. The difference between the two groups was considered significant when $p < 0.05$ in the 95% confidence interval for all statistical analyses.

RESULTS

Seventy-three point eight percent of the children were in the age group of 7-11 years, 26.2% were in the age group of 12-17 years, the average age was 9.8 ± 2.6 . 51.5% of them are girls. It was found that 99% of the children continued their education when one child left the school in high school. Thirty-six point nine percent of the parents stated that the children

Table 1. Parents' opinions for the being affected status of children's daily activities by asthma and affected areas

Opinions	Number	%
Being affected status of daily activities		
Yes	81	78.6
No	22	21.4
Affected fields*		
Inability to play game	67	65.0
Irregular attendance to courses	47	45.6
Intermittent sleep	45	43.7
Decreased appetite	26	25.2
Inability to run fast	13	12.6
Inability to enter physical education courses	9	8.7
Increased appetite	7	6.8

*The parents who indicated that their children's daily activities were affected by the disease, responded more than once to the affected fields.

experienced failures in their courses. In 6.8% of children, the duration after the diagnosis of asthma was 3-11 months, 1-3 years in 30.1% of them, 4-6 years in 35% of them, 7-9 years in 19.4% of them and over 10 years 8.7% of them.

Thirty-eight point eight percent of the children were hospitalized because of asthma, 85% of them were hospitalized 1-5 times. When asthma excretion cases were examined, it was determined that 75.7% of them had asthma attacks, 92.0% of these children had 1-5 attacks. When the occurrence rate of asthma in children was analyzed, 74.8% of them experienced less than once a week, 5.8% of them experienced a few times a week, 15.5% of them experienced every day and, 3.9% of them continuously experienced. When 90.3% of parents stated that their children used continuous medication for asthma treatment, the rate of regular users of medication was found as 78.6%. When parents were asked for feeling differences of their asthmatic children from their peers, 68.9% of them stated that they did not feel any difference. The children who feel themselves different from their peers stated these differences as: attending to the school, participating in sports activities, being with pets, going to the hospital and using medication.

In 67% of the children, asthma symptoms were triggered by cigarette smoke, the asthma symptoms were triggered by house dust mites in 66% of them, the asthma symptoms were triggered by pollen in

57.3% of them, the asthma symptoms were triggered by air pollution in 46.6% of them, the asthma symptoms were triggered by animals in 11.7% of them, the asthma symptoms were triggered by psychological factors in 11.7% of them, the asthma symptoms were triggered by humidity in 9.7% of them, the asthma symptoms were triggered by mold in 5.8% of them and the asthma symptoms were triggered by cockroach in 4.9% of them. In addition to these factors, 40.8% of the parents stated that perfume odor, detergent odor, respiratory tract infection, grass odor, bleach odor, wool, hot air, acidic drinks and strawberry were among the things that trigger asthma symptoms in children.

Eighty-six point four percent of the parents were mothers, 13.6% of them were fathers. 96.1% of the parents stated that they were married and 3.9% stated that they were divorced. When the ages of the mothers were analyzed, 27.0% of them were between the ages

Table 2. Children's quality of life scale average scores

Fields	Min-Max	X ± SS
Emotional function	8-56	42.94 ± 11.05
Activity limitation	5-35	25.90 ± 5.50
Symptoms	10-70	52.68 ± 12.75
Total Score	23-161	121.53 ± 25.29

of 30-34, 33.7% of them were between the ages of 35-39. Seventy-three point eight percent of them were primary school graduates while 86.4% of them were unemployed. When the ages of the fathers were analyzed, 28.6% of them were between the ages of 40-44 and over 50, and 96.1% of them were employed. 94.2% of the parents lived in the district. Eighty-two point five percent of them stated that their income was equal to their expenses, 14.6% of them stated that their income below their expenses, 95.1% of them had social security. Fifty-seven point three percent of the parents had 4 or less households in their houses, 40.8% of them had 5-7 households in their houses. The mean number of people living in the house was 4.5 ± 1.19 . Eighty-nine point three percent of the parents stated that they had children other than those who were brought to the polyclinic, 74.8% of them stated that

they had other children, 76.7% stated that their other children did not have asthma. Ten point seven percent of the mothers and 45.6% of the fathers were smokers. Eighty-nine point three percent of the parents stated that they got training for asthma, 92.2% of them were educated about asthma-triggering factors. In Table 1, the opinions of the parents who participated in the study on their children's daily activities due to illness and the affected areas were given.

When the characteristics of the home environments of the asthmatic children were analyzed, 96.1% of the parents stated that they did not smoke in their homes. Eighty-eight point three percent of the parents stated that they used combi boilers to heat their homes, 11.7% of them used charcoal sofas. 88.3% of them had no pets, 11.7% of them had pets. 69.9% of them stated that there was no humidity problems in

Table 3. Life quality scale points according to stimulating features that start asthma symptoms in children

Features	Emotional function		Activity limitation		Symptoms		Total	
	\bar{x}	SS	\bar{x}	SS	\bar{x}	SS	\bar{x}	SS
Cigarette smoking								
Yes (n = 69)	41.95	10.94	25.40	5.78	50.46	13.80	117.82	26.68
No (n = 34)	44.50	11.04	26.58	4.74	55.91	10.13	127.00	21.11
<i>t</i> test	1.106		1.032		2.265		1.895	
<i>p</i> value	0.271		0.304		0.026		0.062	
Psychological factors								
Yes (n = 12)	36.33	12.36	22.91	6.31	40.41	15.63	99.66	31.67
No (n = 91)	43.64	10.57	26.17	5.26	53.82	11.75	123.64	23.07
Mann-Whitney U test	346.000		384.500		276.500		299.000	
<i>p</i> value	0.040		0.096		0.006		0.011	
Cockroaches								
Yes (n = 5)	46.20	8.13	29.04	3.04	65.40	4.15	141.00	7.74
No (n = 98)	42.62	11.12	25.61	5.51	51.59	12.86	119.82	12.86
Mann-Whitney U test	205.000		139.500		72.500		109.500	
<i>p</i> value	0.539		0.105		0.008		0.038	

their homes, 30.1% of them stated that they had dampness in their homes, 93.2% of them stated that their houses caught the sun, 98.1% stated that they had a home ventilation. Ninety-nine percent of the parents stated that they took measures against asthma stimulants in their homes.

The children's quality of life of asthmatic children scale was found to be 121.53 ± 25.29 . When mean subgroup scores were evaluated, the lowest mean score was found in the field of activity restriction, it was followed by subgroups of emotional function and symptoms (Table 2).

When the quality of life scale scores were analyzed according to the sociodemographic characteristics of the children, it was found that age, gender, general school success did not affect the

quality of life. No significant effect on the quality of life of the child was observed when the scores of the quality of life scale were taken into account according to the disease characteristics of the child such as the number of asthmatic attacks, the number of hospitalizations due to asthma, the frequency of asthma symptoms. Seventy-nine percent of the children regularly used their medications. The stimulants such as house dust mites, pollen, air pollution, animal, humidity and mold were found to have no effect on the children's quality of life when the stimuli that triggered asthma symptoms were analyzed.

The stimulus such as cigarette smoke, psychological factors, cockroaches found to have different effects on the quality of life of the children

Table 4. Quality of life scale scores according to children's parents' descriptive characteristics

Introducing features	Emotional function		Activity limitation		Symptoms		Total	
	\bar{x}	SS	\bar{x}	SS	\bar{x}	SS	\bar{x}	SS
Number of people living at home								
4 people and below (n = 59)	43.18	10.31	26.71	5.07	53.67	11.45	123.57	23.19
5-7 people (n = 42)	43.21	11.17	24.85	5.76	51.14	14.42	119.21	26.61
8 people or more (n= 2)	22.50	13.43	18.50	0.707	34.00	5.65	75.00	7.07
Kruskal-Wallis analysis	4.053		6.311		3.895		4.993	
p value	0.132		0.043		0.143		0.082	
Asthma in other children								
Yes (n = 26)	42.38	13.13	23.50	5.69	49.73	14.19	115.61	29.09
No (n = 77)	42.93	10.25	26.57	5.20	53.11	12.44	122.62	23.76
Mann-Whitney U test	959.000		680.000		878.500		882.500	
p value	0.752		0.015		0.352		0.368	
Mom's smoking status								
Yes (n = 11)	43.63	11.39	29.54	3.85	55.00	11.13	128.18	23.82
No (n = 92)	42.56	10.98	25.26	5.44	51.75	13.09	119.58	25.25
Mann-Whitney U test	485.000		279.000		449.500		400.500	
p value	0.822		0.015		0.546		0.260	

Table 5. Quality of life scale scores according to influence of daily activities of the child due to illness

Daily activity affects status	Emotional function		Activity limitation		Symptoms		Total	
	\bar{x}	SS	\bar{x}	SS	\bar{x}	SS	\bar{x}	SS
Yes (n = 81)	42.40	10.67	25.43	5.77	50.81	13.50	118.65	25.98
No (n = 22)	44.22	12.22	27.13	3.95	57.59	8.82	128.95	20.95
Mann-Whitney U test	727.000		752.500		643.000		687.000	
<i>p</i> value	0.186		0.264		0.046		0.101	

unlike other stimuli. As indicated in Table 3, the children who encountered with psychological factors, who exposed to cigarette smoke that initiated asthma symptoms had a significantly lower mean symptom subgroup score ($p < 0.05$). The mean score of emotional function subgroup in children who were encountered with psychological factors was also found to be low ($p < 0.05$). In children who were exposed to cockroach stimulus, psychological factors, the total score of the quality of life scale was found statistically significantly lower ($p < 0.05$).

The age of parent, educational status, employment status, income status and the status of getting education about asthma were found to have no effect on the quality of life of the child. As shown in Table 4, the difference between the mean scores of the activity restriction subscale was found to be statistically significant ($p < 0.05$). In a further analysis to determine which subscale determines the difference, the difference was found to be due to the number of people living in the homes between 5-7 and 8 and above ($p = 0.0027$). It was found that no significant difference between the other subscales ($p = 0.0167$). The children who had a sibling with asthma and a mother who did not smoke, were found to have a low mean score for activity restriction subscale ($p < 0.05$).

When the mean score of the quality of life scale and subscale scores were evaluated according to the state of daily activities, the mean total score and subgroup score of the children who did not affected by daily activities were found higher (Table 5). In children who were affected by daily activities due to

disease, the mean symptom subscale score was significantly lower ($p < 0.05$).

When the quality of life scale scores were evaluated according to the characteristics of the home environment, it was found that the heating instrument (combi / stove), humidity status, the status of getting sunlight and house ventilation status had no significant effect on the quality of life of the child. The mean score of emotional function subscale of children with asthma who lived with pets was found significantly higher ($p < 0.05$).

DISCUSSION

The mean total quality of life scale score was found to be higher than the other studies [6, 9, 15, 16]. This can be explained by the fact that most of the parents in the study were trained for asthma (89.3%), they could shape their children's daily life activities in this direction.

Although it was not statistically significant, it was determined that the quality of life was negatively affected by increased time after asthma diagnosis. This finding is also similar to the literature [4, 9, 17], suggests that the children who live with a chronic illness for a long time need more support.

In asthmatic children, there are many factors that trigger asthma. Among these factors, exposure to cigarette smoke is one of the most important factors. In this study, a statistically significant difference was found between the mean score of the symptoms subscale of the children who exposed to cigarette

smoke and the mean score of the symptoms subscale of the children who did not exposed to cigarette smoke ($p < 0.05$). It is known that smoking decrease the quality of life of asthmatic children [4, 6, 17-19]. In the studies, it was found that 1/3 of asthmatic children are affected by smoking at home, cigarette smoke affects total and specific allergen levels and skin tests for allergens, allergic symptoms are correlated with parental smoking, maternal smoking is an important risk factor for asthma, children who have smoker mothers have significantly higher levels of asthma than mothers who did not smoke [20-24]. This finding of our study also supports that cigarette smoke is an important stimulus that induces asthma in children and adversely affects the quality of life. In this study, it was also found that 10.7% of the mothers and 45.6% of fathers were smokers. Although not statistically significant, asthmatic children with a father had a lower quality of life score than non-smokers with asthma ($p > 0.05$). In the study of Gümüş *et al.* [9], there was no significant relationship between smoking in the family and the quality of life. In a study by Murray *et al.* [24], the symptoms of asthma in asthmatic children with smoker mothers were found to be much higher than in asthmatic children with mothers who did not smoke.

In many studies, smoking habit of the mother was related to the child's asthma symptoms [4, 6, 17, 18, 20-22, 24]. In this study, it was found that the children who had smoker mothers, had higher mean activity restriction subscale scores and the difference was statistically significant ($p < 0.05$). This finding suggests that smoker mothers do not smoke in the presence of their children, therefore the quality of life of the child is not adversely affected.

In 11.7% of the children in our study, psychological factors were found to initiate asthma attacks. The children who exposed to psychological factors were significantly lower mean scores in emotional function and symptom subscale and total quality of life scale compared to the children who stated that psychological factors did not initiate an asthma attack ($p < 0.05$). It was stated that regular medication, frequent hospitalizations, asthma attacks, the restriction of activities and falling back from school and courses are stressful factors on asthmatic children [5, 25]. Our findings support that the children who can cope with psychological factors can control

asthma attacks, thus their quality of life is also positively affected.

Four point nine percent of the children were affected by cockroach stimulus that initiate asthma attacks. A statistically significant difference was found between the mean symptom subscale and quality of life total scores of the children whose asthma symptoms were triggered by cockroaches and the mean symptom subscale and quality of life total scores of the children whose asthma symptoms werenot affected by cockroaches ($p < 0.05$). There are studies that found positive correlation between cockroach allergen and asthma symptoms [20, 26]. The children who are affected by cockroach stimuli are rare, but our results are similar to the results of the other studies on the subject, the mean total quality of life and symptom subscale scores were found as high.

When the effect of the number of people living with the asthmatic child in the home on the quality of life, it was determined that an increase the number of people living in the household decrease the mean total quality of life scale and the subscale scores. The difference between the number of people living in the home and the activity restriction subscale scores was found as statistically significant ($p < 0.05$). This significance in the mean activity restriction subscale score suggests that other people in houses also obey the restrictions for the children in order to avoid symptoms of asthma, the absence of asthma symptoms in spite of increased number of people may be related with this. According to the similar studies in the literature, it was found that the number of people living in the home has no effect on the the quality of life of an asthmatic child [6, 9].

It is known that pets exacerbate symptoms in asthmatic patients. In this study, 11.7% of the children with asthma were found to have pets (birds) in their homes. When the mean quality of life and the mean subgroup scores of the children living with pets were analyzed, it was found that the mean scores were higher compared to the children living without pets, the mean score of the emotional function subgroup was also statistically significant ($p < 0.05$). Kurt *et al.* [23] found that respiratory symptoms were more common in the individuals who live near the animal shelter. Tamay *et al.* [27] also showed that the presence of animals in the home increases asthma findings. Demirci and Güler [6] found that there is no

relationship between pets and quality of life at home. The positive effects of pets on the individuals with chronic diseases are stated in the literature [28]. In our study, the children living with pets had higher mean quality of life scores, especially mean emotional function score, this condition may be explained by the fact that the symptoms of asthma in children were not very severe and pets have the positive emotional effects on children.

Asthma affects children's daily lives and activities in different aspects. In our study, 78.6% of the children were found to be affected in terms of the daily activities due to disease. The most affected activity by asthma was found as game activity with 65%. Play is an important part of the child's life and is known to be a valuable contribution to the children's physical, cognitive and psychosocial development. When the other activities that were affected by asthma were analyzed, it was found that 45.6% of them could not attend classes regularly, 43.7% of them had had intermittent sleep, 25.2% of them had decreased appetite, 12.6% of them could not run fast and 8.7% did not attend physical education classes. In the study of Özkaya *et al.* [4], three activities of the children were found to be affected by the asthma, they are running (66%), playing football (36%) and climbing up stairs (27%). Reichenberg *et al.* [29] studied with asthmatic children living in Sweden, it was found that running (74%), gymnastics (30%) and climbing (26%) are affected. In the literature, the most affected activity is running, but gaming activity was found as the most affected activity in this study, this condition may be related with the families' protective, limiting manners.

Our this study determined that the children with asthma who stated that their daily activities were affected compared to the children had lower mean total quality of life scale and subscale scores compared to the children with asthma who stated that their daily activities were not affected. There was a statistically significant difference between the mean symptom subscale score of the children who had affected daily activities by asthma and the mean symptom subscale score of the children who did not have affected daily activities by asthma ($p < 0.05$). It was found that the quality of life of children who could play games, regularly attended their courses, did not lose their appetite and run fast was higher, although this

difference was not statistically significant. These results support that alterations in daily activities due to the disease negatively affect the quality of life of the children.

Limitations

The results can not be generalized because the study was carried out only in one institution. The results reflect self-declarations of the children and their parents.

CONCLUSION

It was observed that the quality of life of the children with asthma is affected by symptoms such as wheezing, shortness of breath, chest tightness and coughing attacks. In this direction, the nurse should maintain continuity of home care by teaching stimulants that initiate symptoms, asthma disease, appropriate and effective drug treatment, self-care to the children and their families. The protective attitude towards the child should be prevented and the child's activities such as play, school, sports should be maintained in accordance with the program determined by the health professional. To inhibit psychological factors' effects such as increasing asthma symptoms and affecting quality of life in a negative way, the autonomy of the child should be maintained to deal with his or her own disease and age specific approach should be applied. When pediatric nurses detect allergens, they should help the family to arrange the environment to reduce the child's association with the allergens that can trigger the seizure.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Assessment of inflammatory parameters in obstructive coronary artery disease and cardiac syndrome X: an evolving value of neutrophil-lymphocyte ratio

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ABSTRACT

Objectives: Atherosclerosis represents an active inflammation that leukocytes play a major role. Neutrophil-lymphocyte ratio (NLR) has been shown as an indicator of systemic inflammation. Our aim was to evaluate inflammatory markers in obstructive coronary artery disease (CAD) and cardiac syndrome X (CSX) and to evaluate NLR in predicting CAD in patients with typical chest pain and coronary risk factors.

Methods: Eighty patients with CSX, 80 patients with obstructive CAD with unstable angina pectoris and a control group of 80 subjects were recruited into the study. Hematologic and biochemical parameters were investigated.

Results: High-sensitive C-reactive protein (hs-CRP) was increased in CAD group and CSX group compared to the control group ($p < 0.001$); however it was comparable between CAD and CSX groups ($p = 0.065$). Mean NLR was higher in CAD group than CSX group and control group that the lowest value was in the control group. In CAD group, hs-CRP was positively correlated with NLR ($r = 0.43, p < 0.001$), and Gensini score ($r = 0.54, p < 0.001$). NLR was also linearly correlated with Gensini score ($r = 0.49, p < 0.001$). In ROC curve analysis, for the NLR of 2.26, NLR values attained 85.5% sensitivity and 43.9% specificity ($p < 0.001$). When cut-off value was taken as 3.05 mg/dL for CRP, CRP values attained 78.7% sensitivity and 43.6% specificity ($p < 0.001$). When cut-off value was taken as $9.5 (\times 10^9/L)$ for white blood cell (WBC), WBC values attained 58.8% sensitivity and 34.3% specificity ($p < 0.001$).

Conclusions: NLR seems to be useful in prediction of obstructive CAD and can be implemented in planning for diagnostic procedures in patients with typical chest pain. Increased CRP, WBC and NLR may give insight about main pathology of CSX. Despite absence of obstructive narrowing in epicardial coronaries, it appears to be salutary to treat CSX due to the similar underlying pathophysiology with obstructive CAD.

Keywords: obstructive coronary artery disease, cardiac syndrome X, neutrophil-lymphocyte ratio

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Atherosclerosis represents an active inflammation in which leukocytes play a major role during the atheromatous plaque formation and progression [1]. The subtypes of white blood cells have been investigated for their roles in atherosclerosis intensively [2]. Mononuclear cells (monocytes, macrophages, T-lymphocytes) have indispensable roles within the atherosclerotic plaques [3]. Neutrophils have functions in leukocyte-platelet aggregate formation and reperfusion injury but also are involved in myocardial infarct healing. Neutrophils and lymphocytes indicate opposing clinical outcomes in acute coronary syndromes (ACS) [4]. The neutrophil-lymphocyte ratio (NLR) was reported as an independent predictor for mortality and myocardial infarction in coronary artery disease [5]. NLR has also been reported as a prognostic marker in non-cardiac disease and in patients undergoing percutaneous coronary intervention. Within the markers of inflammation in coronary artery disease NLR has been reported the greatest predictive power for poor outcomes in patients with coronary artery disease [6-8].

Patients having typical chest pain associated with ischaemic ST-segment changes on exercise stress testing or ischaemic findings at myocardial perfusion scintigraphy and with normal epicardial coronaries in coronary angiography are diagnosed as cardiac syndrome X (CSX) [9]. The prominent mechanism is vascular endothelial dysfunction associated with microvascular inflammation [10].

The aim of the current study was to evaluate the inflammatory, biochemical and haematological parameters in patients with obstructive coronary artery disease (CAD) and CSX and to investigate the predictive role of NLR for CAD and CSX.

METHODS

This study was designed as a cross-sectional and observational study. For this study, totally 630 subjects were reviewed in detail. Eighty patients diagnosed with CSX who were admitted to our hospital, 80 patients with obstructive CAD with unstable angina pectoris and a control group of 80 subjects were recruited into the study between April 2012 and November 2013, after the approval of local ethics

committee. CSX was defined as typical chest pain during rest or effort, abnormal test result for exercise electrocardiography (ECG) and myocardial perfusion scintigraphy and the presence of angiographically normal epicardial coronary arteries. Control group was selected from volunteers presented to our hospital with the complaint of atypical angina who had similar risk profile with the patients (diabetes [DM], hypertension [HT], age, gender) and had normal coronaries at coronary angiography. Patients with valvular heart disease (mitral stenosis and moderate to severe mitral regurgitation, moderate to severe aortic stenosis and regurgitation including mitral annular calcification), heart failure (left ventricular ejection fraction [LVEF] < 50%), congenital heart disease, cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, cardiac surgery, thyroid disease, anemia, infectious or pulmonary diseases were not included into the control group and patient group with CSX. Patients with CAD had single vessel or multivessel disease, according to the number of epicardial arteries with at least one lesion measuring $\geq 50\%$ diameter stenosis and typical angina pectoris in whom cardiac necrosis markers were not elevated.

blood is collected in a tube containing K3 EDTA for measurement of hematologic indices in all patients undergoing the coronary angiography. Hematologic indices are evaluated from complete blood count (CBC) analysis performed by a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc. Mervue, Galway, Ireland). Lipid serum levels were measured immediately by routine methods. Serum total triglyceride (TG) and total cholesterol (TC) were measured by enzymatic methods on an automatic biochemical analyzer. Serum high-density lipoprotein-cholesterol (HDL-C) was tested by magnesium tungstate phosphate sedimentation and the concentration of low-density lipoprotein-cholesterol (LDL-C) was calculated by the Friedewald formula as follows: $LDL-C \text{ (mmol/L)} = TC - HDL-C - TG/2.2$ ($TG < 4.5 \text{ mmol/L}$). Fasting blood samples were also collected in tubes containing citrate, and were drawn and centrifuged immediately. Serum was then aliquoted and stored at -80°C until analysis for C-reactive protein (CRP) measurement. No specimen inadvertently thawed during storage. CRP measurements were performed on the COBAS Integra (Roche Diagnosis Limited, East Sussex, United

Table 1. Clinical characteristics of study groups

Groups	Control (n = 80)	CSX (n = 80)	CAD (n = 80)
Males/Females	40/40	43/37	47/33
Age (years)	47.9 ± 6	49.2 ± 10	61.2 ± 9*
BSA (m ²)	1.78 ± 0.14	1.76 ± 0.16	1.77 ± 0.12
BMI (kg/m ²)	26.5 ± 2.9	27.6 ± 3.5 [†]	27.8 ± 2.4
Systolic blood pressure (mmHg)	120.1 ± 10.7	123.6 ± 9.3	122.6 ± 13.6
Diastolic blood pressure (mmHg)	74.2 ± 7,4	73.6 ± 5,2	74.2 ± 9
Heart rate (bpm)	76 ± 8	74 ± 10	81 ± 13 [†]
Smoking, n (%)	28 (35%)	30 (37%)	33 (41%)
Hypertension, n (%)	33 (41%)	34 (42%)	36 (45%)
Diabetes mellitus, n (%)	25 (31%)	20 (25%)	25 (31%)
Hyperlipidemia, n (%)	26 (32%)*	22 (28%)	52 (65%)* [‡]
LVEF (%)	61.1 ± 3.0	60.4 ± 2.8	47.3 ± 9.7* [‡]
Gensini score	-	-	21.45 ± 15.49

Data are shown as mean ± standard deviation or number (percent). BMI = body mass index, BSA = body surface area, CAD = coronary artery disease, CSX = cardiac syndrome X, LVEF = left ventricular ejection fraction, * $p < 0.001$ versus control group, [‡] $p < 0.001$ versus CSX group, [†] $p < 0.05$ versus control group

Kingdom) using the CRP-latex assay in both the high-sensitivity application (analytical range, 0.2 to 12 mg/l) and the normal application (analytical range, 2 to 160 mg/l).

Statistical Analysis

Body mass index (BMI) was calculated by the common formula: BMI (kg/m²) = weight (kg)/height (m²). Body surface area (BSA) was assessed by a variation of the DuBois and DuBois formula: BSA (m²) = [weight (kg)0.425 × height (cm)0.725] × 0.007184 [11]. Patient demographic characteristics are presented as means and standard deviations for continuous variables and as proportions (percentages) for categorical variables. To test the distribution pattern, the Kolmogorov–Smirnov test was implemented. Comparisons of multiple mean values were carried out by Kruskal–Wallis tests or Analysis of Variance as appropriate. Categorical variables were

compared with Chi-square test. Relationships between variables were examined by Pearson's correlation coefficient. Threshold values of the receiver operating characteristic (ROC) analysis were statistically significant. The level of significance set at $\alpha = 0.05$. Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS version 20.0, SPSS Inc., Chicago, IL, USA).

RESULTS

The clinical characteristics of the study groups were listed in Table 1. While there was no significant difference for gender between CSX group and CAD group ($p = 0.838$) and between CSX group and control group ($p = 0.062$), there was significant difference between control group and CAD group ($p = 0.020$). Control and CSX groups were significantly younger

Table 2. Laboratory findings

Groups	Control (n = 80)	CSX (n = 80)	CAD (n = 80)
Glucose (mg/dL)	92.4 ± 3.3	94.3 ± 5.6	98.2 ± 8.1
Total cholesterol (mg/dL)	177.5 ± 35.9	183.6 ± 49.3	196.7 ± 45.8 ^φ
HDL-C (mg/dL)	47.3 ± 12.2	43.1 ± 10.3*	43.9 ± 13.4*
LDL-C (mg/dL)	100.5 ± 24.2	103 ± 33.8	126 ± 37.3 ^{†θ}
TG (mg/dL)	167.9 ± 36.1	171.6 ± 68	174.4 ± 43
WBC (/mm ³)	7.56 ± 1.08	8.19 ± 1.53*	9.92 ± 2.33 ^{†θ}
Neutrophil (10 ¹² /L)	4.96 ± 1.35	5.87 ± 2.17 [‡]	6.18 ± 1.28 [†]
Lymphocyte (10 ¹² /L)	2.62 ± 0.79	2.47 ± 0.80	1.89 ± 0.63 ^{†θ}
NLR	1.87 ± 0.52	2.67 ± 0.84 [†]	3.63 ± 0.38 ^{†θ}
Erythrocyte (10 ¹² /L)	4.5 ± 0.4	4.7 ± 0.8	4.9 ± 0.2
Hemoglobin (g/dl)	13.92 ± 1.5	14.0 ± 1.81	13.38 ± 3.5
MCV (fL)	86 ± 3.2	85 ± 2.6	83 ± 3.1
Platelet	231125 ± 40689	237500 ± 59149	235700 ± 59251
MPV	8.03 ± 0.65	8.37 ± 0.89 ^β	8.69 ± 0.88 ^{†♥}
CRP (mg/dL)	2.34 ± 1.6	5.41 ± 1.39 [†]	7.62 ± 2.58 ^{†♥}

Data are shown as mean ± standard deviation. CAD = coronary artery disease, CRP = C-reactive protein, CSX = cardiac syndrome X, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol, MCV = mean corpuscular volume, MPV = mean platelet volume, NLR = neutrophil-lymphocyte ratio, TG = total triglyceride, WBC = white blood cell, * $p < 0.05$ versus control group, [†] $p < 0.001$ versus control group, ^β $p < 0.01$ versus control group, [‡] $p < 0.005$ versus control group, ^φ $p < 0.005$ versus control group, [♥] $p < 0.05$ versus CSX group, ^θ $p < 0.001$ versus CSX group

compared to the CAD group ($p < 0.0001$), however there was no significant difference for mean age between the control group and CSX group ($p = 0.667$). Heart rate per minute was comparable between the CSX and control groups ($p = 0.409$), but was significantly higher in CAD group compared to the control group ($p = 0.011$) and CSX group ($p < 0.001$). There was no significant difference for BMI between the study groups. Systolic and diastolic arterial pressures were similar among all study groups. Smoking, HT and DM incidences were similar among the study groups. The hyperlipidemia incidence was higher in CAD group compared to the control and CSX groups. In the transthoracic echocardiography,

LVEF was comparable between the CSX and the control groups; but LVEF was significantly lower in CAD group as compared to the other two groups. The severity of ischaemic heart disease using Gensini score for the group with CAD was shown in Table 1.

The haematologic and biochemical parameters of the study groups were shown in Table 2. There was no difference for glucose between the groups. Total cholesterol was similar between CAD and CSX groups; but it was significantly higher in CAD group than in control group. TG levels were similar between the study groups. LDL-C was not different between the control group and CSX group; but was significantly higher in CAD group. HDL-C was

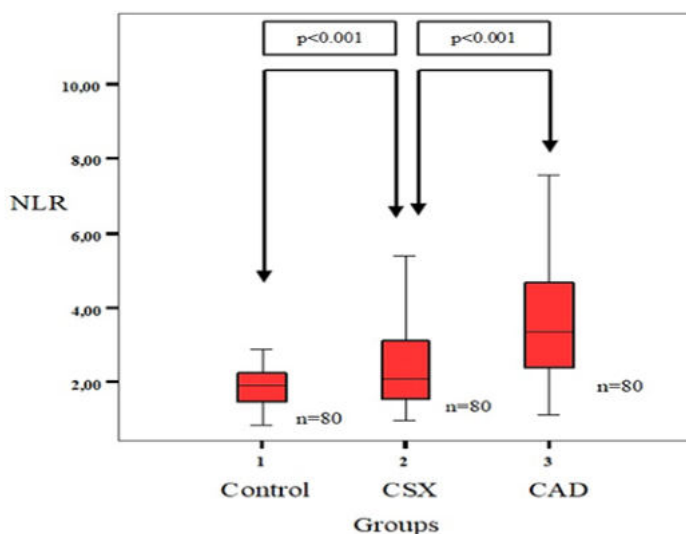


Fig. 1. Neutrophil-lymphocyte ratio of the study groups.

significantly found to be decreased both in CAD and CSX groups. There was no significant difference for haemoglobin, hematocrit and platelet counts between the study groups. Mean platelet volume (MPV) was significantly higher in CAD group compared to the other two groups; also it was higher in CSX group than in the control group. White blood cell (WBC) was higher in CAD group than CSX group ($p < 0.001$) and was higher in CSX group than control group ($p = 0.022$). There was no significant difference for neutrophil counts between CAD and CSX groups ($p = 0.201$); however, neutrophil count was significantly higher in CAD ($p < 0.001$) and CSX ($p = 0.012$) groups than control group. Regarding the lymphocyte

counts, there was no significant difference between the control group and CSX group ($p = 0.493$), but lymphocyte count in patients with CAD group was significantly lower than CSX and the control groups. Consequently, NLR was significantly different between the study groups; NLR was higher in CAD group than CSX group and the control group that the lowest mean value was reported in the control group (Fig. 1). CRP levels were significantly different between the study groups; CRP was significantly found to be increased in CAD group and in the CSX group compared to the control group ($p < 0.001$), however it was comparable between the CAD and CSX groups ($p = 0.065$).

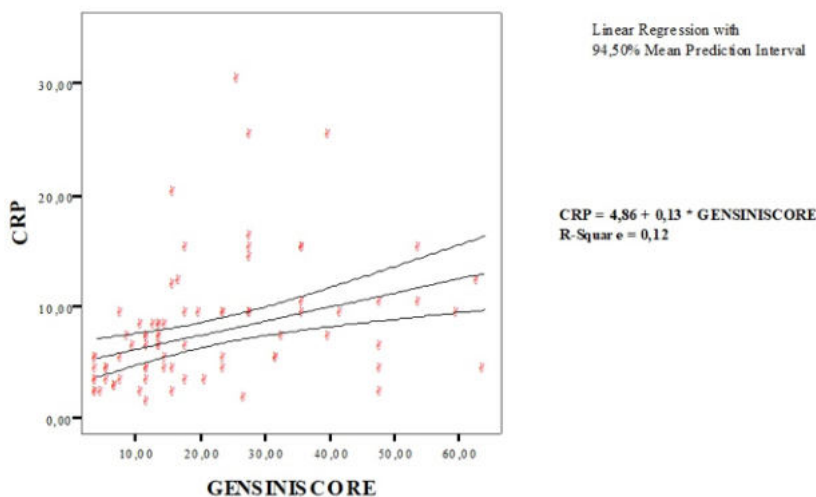


Fig. 2. Correlation of CRP and Gensini score in CAD group. CAD = coronary artery disease, CRP = C-reactive protein

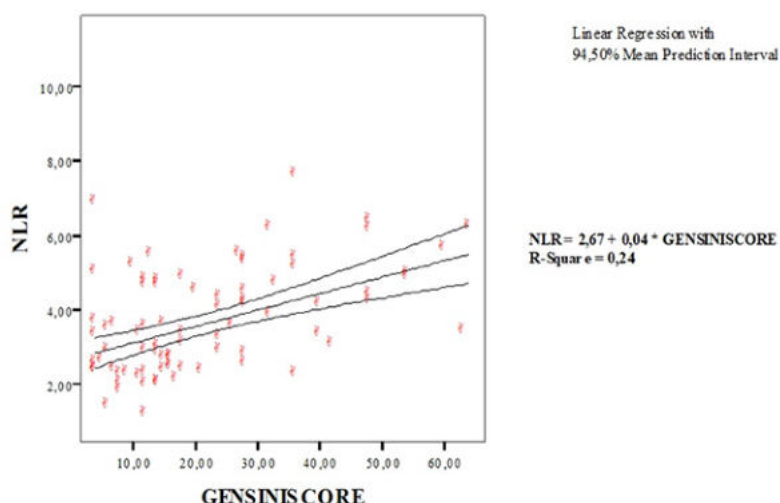


Fig. 3. Correlation of NLR and Gensini score in CAD group. CAD = coronary artery disease, NLR = neutrophil-lymphocyte ratio

In CSX, CRP was significantly positively correlated with the neutrophil count ($r = 0.40, p < 0.001$), fairly negatively correlated with the lymphocyte count ($r = -0.18, p = 0.077$), significantly positively correlated with NLR ($r = 0.38, p = 0.001$), significantly positively correlated with WBC ($r = 0.489, p < 0.001$). NLR was in a significant linear correlation with total cholesterol, TG and LDL-C ($r = 0.37, p = 0.001$; $r = 0.33, p = 0.006$; $r = 0.38, p =$

0.001 , respectively). In CAD group, CRP had significant linear correlation with WBC count ($r = 0.33, p < 0.005$) and was also significantly positively correlated with NLR ($r = 0.43, p < 0.001$) and with Gensini score ($r = 0.54, p < 0.001$) (Fig. 2). In the group of CAD, NLR was also significantly correlated with Gensini score ($r = 0.49, p < 0.001$) (Fig. 3).

The ROC curve analysis was performed to compare the abilities of CRP, WBC and NLR in

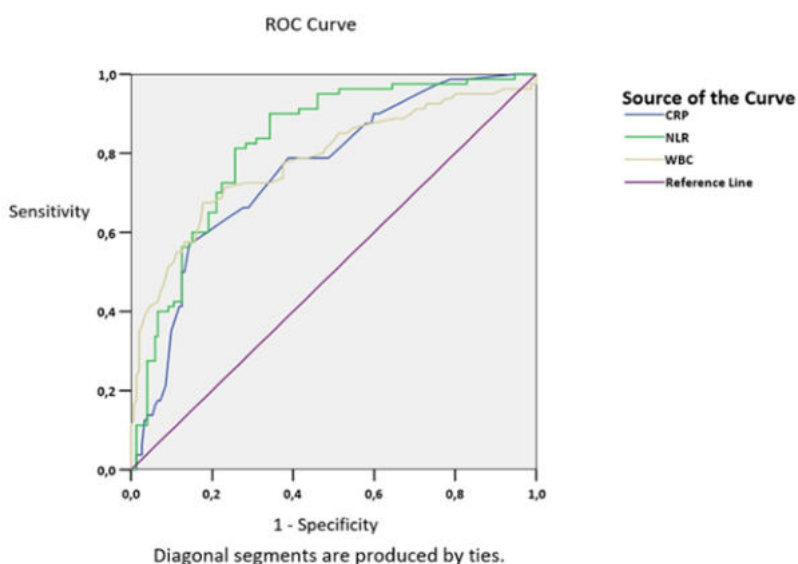


Fig. 4. ROC curve analysis for the ability of NLR, CRP and WBC to predict obstructive CAD in patients with chest pain. For NLR; the area under the curve (AUC) is 0.823 (95% confidence interval [CI]: 0.768-0.878). NLR = 2.26; the sensitivity was 85.5% and the specificity was 43.9.6%. For WBC, the AUC is 0.781 (95% CI: 0.714-0.849). WBC = 9.5 ($\times 10^9/L$); the sensitivity was 58.8% and the specificity was 34.3%. For CRP, the AUC is 0.756 (95% CI: 0.692-0.820). CRP = 3.05 mg/dL; the sensitivity was 78.7% and the specificity was 43.6%. CAD = coronary artery disease, CRP = C-reactive protein, NLR = neutrophil-lymphocyte ratio, ROC = receiver operating characteristic, WBC = white blood cell

predicting obstructive coronary artery disease including coronary artery narrowing > 50% of the coronary vessel diameter in patients with typical chest pain. We examined the sensitivity and specificity of CRP, WBC and NLR for detection of coronary artery disease at different CRP, WBC and NLR values; whereas NLR provided excellent sensitivity and specificity for the detection of obstructive coronary artery disease. In patients of the three groups, when the cut-off value was taken as 2.26 for NLR, NLR values attained a 85.5% sensitivity and 43.9% specificity ($p < 0.001$). When the cut-off value was taken as 3.05 mg/dL for CRP, CRP values attained a 78.7% sensitivity and 43.6% specificity ($p < 0.001$). When the cut-off value was taken as 9.5 ($\times 10^9/L$) for WBC, WBC values attained a 58.8% sensitivity and 34.3% specificity ($p < 0.001$) (Fig. 4). It seems that NLR significantly predicted obstructive coronary artery disease in patients with chest pain.

DISCUSSION

The main finding of our study was that, NLR, CRP and WBC were significantly increased in patients with obstructive CAD compared to the patients with CSX and control group. Additionally, in patients with CSX, NLR, CRP and WBC were significantly increased compared to the control group. NLR was found significant in determining obstructive coronary artery disease in patients with typical chest pain and coronary risk factors.

The role of inflammation in CAD has been shown in several studies [12]. CRP, that's the prototype of acute phase proteins, is a marker of systemic inflammation, elevated in response to injury, infection, and various inflammatory stimuli [13]. CRP is related to some cardiovascular risk factors, such as obesity, smoking, increased blood pressure, serum lipids, increased blood glucose, and inversely to HDL-C levels [14, 15]. CRP was also reported as an important biomarker in predicting obstructive CAD [16]. In the current study, CRP was significantly increased in patients with CSX and obstructive CAD as compared to the control group; there was no significant difference for CRP between patients with obstructive CAD and patients with CSX. This finding implicated that CSX has an inflammatory underlying pathology.

In several previous studies, systemic inflammation was found related with microvascular endothelial dysfunction which has been proposed as the main pathophysiological mechanism of CSX [17]. Inflammation that can be assessed with CRP, has a significant detrimental effect during the impairment of endothelium-dependent vasodilator function in patients with CSX [18]. Teragawa *et al.* [19] investigated the relation between CRP concentrations and coronary microvascular endothelial function in patients with chest pain and angiographically normal coronary arteries. They found inverse and independent correlation between CRP levels and acetylcholine-induced changes in coronary blood flow. In the study of Tousoulis *et al.* [20] the researchers reported increased blood levels of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), adhesion molecules that are synthesized by activated endothelial cells in response to inflammatory stimuli, in patients with cardiac syndrome X.

NLR reflects the balance between neutrophil and lymphocyte levels in peripheral blood and recently has been shown as an indicator of systemic inflammation [21]. In various studies, higher NLR value has been reported be associated with adverse clinical outcomes in patients with CAD. During the hospitalization, NLR was an independent predictor of in-hospital and 6-month mortality in patients with ACS. NLR was also an independent predictor of 1- and 6-month and 4-year mortalities in patients with non-STEMI and ST-elevated myocardial infarction (STEMI) [22, 23]. In our observational study, NLR was significantly increased in patients with obstructive CAD when compared to patients with CSX and control group. Furthermore, NLR was significantly increased in patients with CSX compared to the control group. This result stated that, beside the CRP, NLR was also useful in prediction of obstructive CAD in patients with typical chest pain. Additionally, this simple readily available marker may provide a risk stratification in patients with typical anginal chest pain beyond the conventional risk scores.

Limitations

Our study has some limitations which should be mentioned. First, the study population was relatively small. Second, an intravascular imaging was not

carried out at baseline assessment. Therefore, it was unknown whether any of the patients with CSX had atherosclerosis not identifiable by coronary angiography. Third, we did not perform measurements related with endothelial dysfunction in patients with CSX. Fourth, we could not measure levels of inflammatory proteins (i.e., TNF α , IL-6) because of lack of technical facilities in our center.

CONCLUSION

NLR is useful in prediction of obstructive coronary artery disease in patients with typical anginal chest pain and conventional risk factors. In patients with CSX, increased CRP, WBC and NLR may give insights about the main pathology of this disease. Despite the absence of evident obstructive narrowing in epicardial coronaries, it seems salutary to treat CSX, since it has the same underlying pathophysiology with obstructive CAD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Nephrotoxicity rates related to colistin and evaluation of risk factors

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ABSTRACT

Objectives: Colistimethate sodium (colistin) is the member of polymyxins, the cyclic structured cationic polypeptide antibiotics. The purpose of our study is to determine the patients' nephrotoxicity rates and risk factors related to nephrotoxicity development that are under colistin treatment in the tertiary intensive care unit (ICU).

Methods: One-hundred colistin received patients files were reviewed retrospectively, who were in tertiary ICU in Bursa Yüksek İhtisas Training and Research Hospital. Fifteen patients with the history of renal failure were excluded from the study. The data before the first colistin treatment was taken into consideration for the patients received repetitive colistin treatment. RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification was used for the evaluation of nephrotoxicity.

Results: The patients mean age was 67.81 ± 16.56 years (range: 21-94) and 52.9% were male. Nephrotoxicity was determined in 35 (41.2%) patients. According to the RIFLE classification the nephrotoxicity rates were determined for risk, injury and deficiency were 24.7%, 10.6% and 5.9%, respectively. Nephrotoxicity was detected in 9 (25.7%) out of 35 patients on the first day of the colistin treatment. Mortality rate was observed as 82.9% in patients with nephrotoxicity.

Conclusions: Colistin treatment is preferable for the treatment of multi drug resistant infections in intensive care unit. The patients, under certain circumstances, i.e., malignancy, using additional nephrotoxic agent and elder age must be closely monitored for the possible nephrotoxicity development.

Keywords: colistin, nephrotoxicity, RIFLE score

Colistimethate sodium (colistin) is a member of the cyclic structured cationic polypeptide antibiotics, polymyxins. The polymyxins which are discovered in 1947, were used for the treatment of the gram-negative bacterial infections since 1962 [1, 2]. Colistin use was decreased gradually, because of its nephro-

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toxicity and several new antibiotics with gram negative effects were taken a place since 1980s. The increase of multiple drug resistant gram negative bacterial infections brings the colistin treatment back to the agenda.

The nephrotoxicity during the colistin treatment is dose dependent and reversible. The increase of colistin concentration by tubular reabsorption and proximal tubular injury is held responsible for the nephrotoxicity. Nephrotoxicity is a serious contraindication to quit the treatment [3, 4].

The purpose of our study is to determine the patient's nephrotoxicity rates and risk factors related to nephrotoxicity development who are under colistin treatment in the tertiary intensive care unit (ICU).

METHODS

Patients older than 18 years who received at least 24-hour colistin treatment in Bursa Yüksek İhtisas Training and Research Hospital's tertiary ICU were enrolled to this study. Six patients with acute renal failure and 9 patients with chronic renal failure were excluded from the study. The patient's data were reviewed from their medical records and ICU follow-up forms, retrospectively. The patients' diagnosis, demographic data (age and sex), additional diseases, the existence of malignancy, type of infection, detected microorganisms, duration of hospitalization, APACHE2 (Acute Physiology and Chronic Health Evaluation) scores at the first day of the colistin treatment and daily creatinine values, the need

Table 1. Demographic and clinical features of the patients

Patients features	All patients mean ± SD or n (%)	Nephrotoxicity developed patients mean ± SD or n (%)	Nephrotoxicity not developed patients mean ± SD or n (%)	p value
Demographic features				
Age (year)	67.81 ± 16.56	69.94 ± 16.56	66.32 ± 17.40	0.48
Sex (male/female)	45/40 (52.9/47.1)	20/15 (57.1/42.9)	25/25 (50/50)	0.51
Additional diseases				
Neurologic disease	44 (51.8)	15 (42.9)	29 (58)	0.16
Cardiac disease	35 (41.2)	10 (28.6)	25 (50)	0.65
COPD	19 (22.4)	8 (22.9)	11 (22)	0.92
Hypertension	18 (21.2)	7 (20)	11 (22)	0.82
Diabetes mellitus	13 (15.3)	7 (20)	6 (12)	0.16
Malignancy	6 (7.1)	5 (14.3)	1 (2)	0.03
Need of positive inotrop	62 (72.9)	29 (82.9)	33 (66)	0.08
Mortality	59 (69.4)	29 (82.9)	30 (60)	0.02
APACHE II score				
In the acceptance to intensive care unit	23.16 ± 5.24	22.94 ± 5.20	23.33 ± 5.34	0.75
In the first day of the colistin treatment	24.54 ± 6.87	24.64 ± 6.65	24.48 ± 7.10	0.80

COPD = Chronic obstructive pulmonary disease, APACHE = Acute Physiology and Chronic Health Evaluation

for hemodialysis and inotrope therapy during the treatment were all recorded. The data before the first colistin treatment was taken into consideration for the patients received repetitive colistin treatment. Concurrently used drugs, like; carbapenem, glycopeptide, vancomycin, aminoglycoside and diuretics were noted. RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification was used for nephrotoxicity evaluation.

Statistical Analysis

Chi-square analysis was used for evaluation of categorical variables. The t-test or corresponding non-parametric test was used for analysis of continuous variables. A *p* < 0.05 value was accepted as statistically significant for all analyses.

RESULTS

Eighty-five patients were included to the study. Sixty-eight of them have additional diseases and 6 patients have malignancy. Demographic and clinical features of the patients were given on the Table 1.

Nephrotoxicity developed in thirty-six (41.2 %) patients. According to the RIFLE criteria risk, injury and failure rates were found as 24.7%, 10.6%, 5.9%, respectively (Table-2). Nephrotoxicity was developed in 9 (25.7%) patients on the first day of the treatment. Twenty-two (62.9 %) patients developed nephrotoxicity in the first week. Mortality rates after colistin treatment was determined as 82.9% in the nephrotoxicity developed group and 60% in the others,

Table 2. The nephrotoxicity rates according to the RIFLE score

Criteria	Number of patients (%)
No risk	50 (58.8)
Risk	21 (24.7)
Injury	9 (10.6)
Failure	5 (5.9)
Total	85 (100)

RIFLE = Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease

the difference were statistically significant (*p* = 0.02).

When assessed for accompanying diseases, 51.8% of the patients had neurological disease and 41.2% had cardiac disease. Nephrotoxicity rate was 40.3% in patients with accompanying disease and 44.4% in patients without accompanying disease (*p* = 0.75).

Nephrotoxicity rate (83.3%) was significantly higher in patients with malignancy than in those without malignancy (*p* = 0.03). Concomitant use of aminoglycoside, glycopeptide, vancomycin, carbapenem and diuretic was higher in the group with nephrotoxicity (Table 3). Although, the need for inotropic agent higher in nephrotoxicity developing group (46.8 vs. 26.1%), it was not statistically significant (*p* = 0.08). Hemodialysis is required in 17.1% of the patients who has nephrotoxicity.

The number of patients treated with colistin for pneumonia, bacteremia, wound infection, urinary

Table 3. The relationship between concurrent drug use and development of nephrotoxicity

Concurrent use of drug	All patients n (%)	Nephrotoxicity developed patients; n (%)	Nephrotoxicity non developed patients n (%)	<i>p</i> value
Diuretic	56 (65.9)	26 (74.3)	30 (60.0)	0.17
Carbapenem	52 (61.2)	22 (62.9)	30 (60.0)	0.79
Vancomycin	11 (12.9)	6 (17.1)	5 (10.0)	0.44
Glycopeptide	10 (11.8)	3 (8.6)	7 (17.0)	0.33
Quinolone	9 (10.6)	2 (5.7)	7 (14.0)	0.22
Aminoglycoside	2 (2.4)	1 (2.9)	1 (2.0)	0.79

system infection and catheter related infections are 60, 17, 5, 1 and 1, respectively. *Acinetobacter baumannii* (72.9%), *Pseudomonas aeruginosa* (14.1%) and *Klebsiella spp.* (7.6%) were isolated most frequently.

DISCUSSION

The use of colistin is currently recommended only in infections caused by gram-negative microorganisms with multiple drug resistance and particularly in the presence of antibiotic resistance except colistin. For this purpose, it can be used especially for hospital-acquired pneumonia, bacteremia, surgical site infections, catheter infections and urinary system infections caused by resistant gram-negative bacteria, as well as in the treatment of patients with cystic fibrosis and in the treatment of *P. aeruginosa* infections in transplantation patients [1, 2]. In our study, we observed that it is most commonly used for the treatment of patients with pneumonia caused by *Acinetobacter baumannii*.

The nephrotoxicity development rate in patients treated with colistin in ICU has been reported to be 10-50% [3-8]. The different rates of nephrotoxicity in the researches may be related with using different renal failure diagnosis criteria. Today, RIFLE criteria are preferred in acute renal failure (ARF) classification [9]. In our study, we observe nephrotoxicity rates 41.2% rates with using RIFLE criteria in accordance with the literature [6-8].

Nephrotoxicity time was not determined throughout the studies. It has been reported that nephrotoxicity generally developed within the first five to seven days in the majority of nephrotoxicity time given studies [8, 10, 11]. In our study, nephrotoxicity was detected in 25.7% of the patients on the first day of treatment and in 62.9% of patients within the first seven days of colistin treatment, in accordance with the literature.

Cytotoxic agents, nephrotoxic drugs, risk of sepsis or organ infiltration may cause renal injury, but direct renal infiltration of malignancy may also result in ARF [12-14]. Darmon *et al.* [14] reported that the rate of ARF development was 12-49% in patients with malignancy and followed up in ICU. Hachem *et al.* [15] found that 23% of patients with malignant disease developed nephrotoxicity as a result of the use of colistin in the treatment of *pseudomonas* infections.

The rate of nephrotoxicity was significantly higher in patients with malignancy in our study ($p = 0.03$). This data is consistent with other studies [16, 17].

In many studies, elder age, addition of drugs such as vancomycin, aminoglycoside, carbapenem, diuretic and non-steroidal anti-inflammatory drugs, the use and duration of colistin usage has been reported as the risk factors for the development of colistin nephrotoxicity [3, 18-20]. In our study, nephrotoxicity was found to be more common with the age, aminoglycoside, diuretic, carbapenem, glycopeptide and vancomycin simultaneous use, but the difference was not statistically significant.

In our study mortality rate was significantly higher in the nephrotoxicity developed group parallel to some other studies in the literature ($p = 0.02$) [16, 21, 22]. The inotropic need was found to be higher in the nephrotoxicity-developing group, but the difference was not statistically significant ($p = 0.08$). Kaya *et al.* [16], found that the inotropic requirement was higher in the group with nephrotoxicity. Studies evaluating inotropic need in the literature are insufficient and we think that our findings are important for the contribution to the literature.

Limitations

Limitations of our study; single centered, retrospective study and the number of patients is small. There is a need for prospective studies with large patient group.

CONCLUSION

In conclusion, colistin treatment can be preferred for the treatment of the multiple resistant pathogens in ICU patients but during the treatment of elderly patients, malignancy, additional nephrotoxic agent must be followed up closely especially in the first day and first week for the development of nephrotoxicity.

Conflict of interest

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The prognostic role of Charlson comorbidity index for critically ill elderly patients

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ABSTRACT

Objectives: Comorbidities represent a risk factor for adverse events in several critical illnesses. The aim of this study was to identify the relationship between the Charlson Comorbidity Index (CCI) with mortality and length of stay (LOS) in critically ill elderly patients.

Methods: A retrospective analysis was made of patients admitted to our tertiary adult intensive care unit (ICU) between January 2015 and January 2016. The impact of comorbidity was evaluated with the CCI. Other required data were retrieved from the patients' follow-up records.

Results: The study included a total of 251 patients. The mean age was 78.79 ± 6.70 years. The total mortality rate was 41.0%. The most common cause for admission was sepsis and acute respiratory failure (18.3% vs 18.3%). The median APACHE II score was significantly higher in non-survivors than survivors (31.0 [13.0-47.0] vs 21.0 [9.0-40.0]; $p < 0.01$). The median CCI was 2.0 (0.0-7.0) for survivors and 3.0 (1.0-10.0) for non-survivors. The CCI of non-survivors was significantly higher than that of survivors ($p = 0.005$). Patients with CCI > 3 had higher mortality than those with CCI ≤ 3 ($p < 0.05$). The odds ratio of the APACHE II score for mortality was 1.214 (95% CI: 1.154-1.276), and for CCI it was 1.320 (95% CI: 1.088-1.602). There was a significant positive correlation between CCI and LOS ($r = 0.147$; $p = 0.020$).

Conclusions: CCI is strongly associated with both mortality and LOS. It can be used as a prognostic marker for elderly patients in critical care.

Keywords: Charlson comorbidity index, older patients, critically ill, mortality

There are many prognostic factors and scoring systems for mortality and prognosis in ICU patients. Of these, the Acute Physiology and Chronic Health Evaluation (APACHE) score is one of the most frequently used scoring systems [1]. In recent years, there has been increasing interest in different indicators which may be useful for the prediction of mortality.

Population aging and the increasing frequency of chronic diseases has created a greater need for acute

healthcare services, with an increased number of elderly patients admitted to ICU [2]. Comorbidity is one of the major factors affecting health status and management strategies in critically ill patients especially the elderly [3]. The coexistence of two or more long-term pathologies is defined as multimorbidity, and this condition is related to frailty, disability, increased risk of hospitalization and death, especially among elderly patients [4].

The Charlson Comorbidity Index (CCI), first re-

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ported in 1987, is a commonly used index which is used for predicting prognosis based on comorbid conditions of the patient [5]. The CCI was subsequently shown to be important and effective prognostic marker for mortality in many diseases and conditions [6, 7]. The aim of this study was to present the prognostic value of the CCI for mortality and length of stay (LOS) in older patients admitted to the Internal Medicine Adult ICU of Karabuk University Training and Research Hospital.

METHODS

A retrospective analysis was made of patients admitted to the Medical ICU of Karabuk University Training and Research Hospital from January 2015 to January 2016. Patients with a length of stay (LOS) of less than 48 hours and younger than 65 years age were excluded. The study included a total of 251 patients aged > 65 years.

Evaluation was made of the demographic information, laboratory test results, APACHE II scores, and diagnosis at the time of admission. Comorbidity was defined as pre-existing diseases and medical conditions present at the time of admission. The comorbidities and conditions of the patients were recorded. The CCI score was calculated using these parameters. Table 1 shows the list of comorbid conditions included in the CCI. For the analyses, the study population was separated into 2 groups as survivors and non-survivors.

Compliance with Ethical Standards

All procedures performed in the 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.

Statistical Analysis

SPSS Statistics 19 software (IBM, Armonk, NY, USA) was used for statistical analysis. In the comparison of variables distributed homogeneously, the t-test was used for parametric variables and the Chi-Square test was used for non-parametric variables. For variables not showing homogeneous distribution, the Mann Whitney U test was used. Data were

expressed as mean \pm standard deviation (SD) and median (minimum-maximum) values. Multiple logistic regression analyses were used to determine the risk factors for mortality and LOS. Kaplan–Meier survival curves was used for survival analysis. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

The total 251 patients comprised 109 males (43.4%) and 142 females (56.6%) with a mean age of 78.79 ± 6.70 years. A total of 103 (41.0%) patients died during the follow-up period and 148 (59.0%) patients survived and were either transferred to other departments in the hospital or discharged. The demographic data are shown in Table 2. The most common diagnoses for ICU admission were acute respiratory failure (18.3%), sepsis (18.3%) and pneumonia (15.9%). Median overall survival was 17 days (14.9-19.1) (Fig. 1).

Table 1. Charlson Comorbidity Index

Condition or disease	Comorbidity Score
Coronary artery disease	1
Congestive heart failure	
Peripheral vascular disease	
Cerebrovascular disease	
Dementia	
Chronic pulmonary disease	
Connective tissue disorder	
Peptic ulcer disease	
Mild liver disease	
Diabetes	
Hemiplegia	2
Moderate or severe renal disease	
Diabetes with end-organ damage	
Any tumor, leukemia, lymphoma	
Moderate or severe liver disease	3
Metastatic solid tumor	6
AIDS	

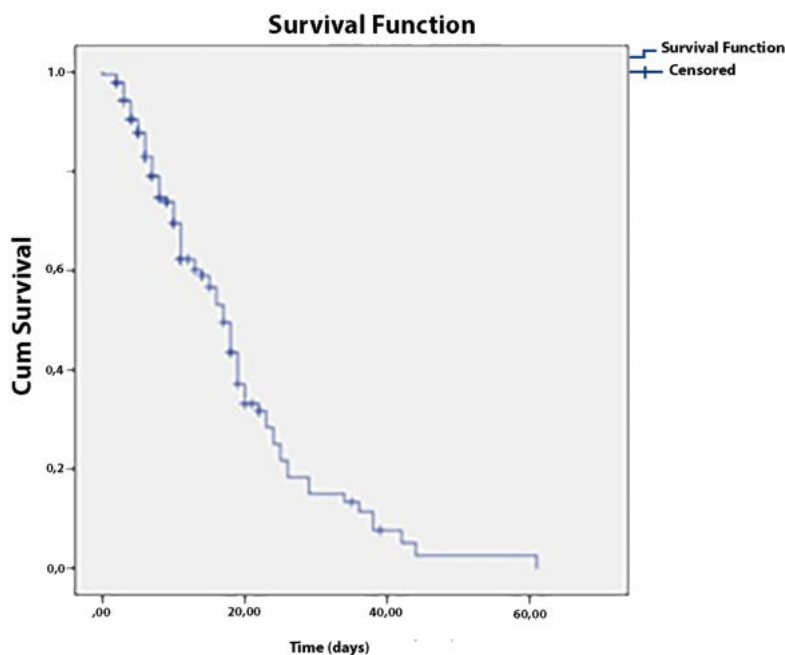


Fig. 1. Kaplan-Meier survival analysis for overall survival of the patients

The median age was 80.0 years (65.0-93.0) for non-survivors, which was higher than that of survivors at 79.5 years (65.0-99.0), but not statistically significant ($p = 0.975$). The median APACHE II score of the whole patient group was 26.0 (9.0-47.0). It was significantly higher in non-survivors than survivors (31.0 [13.0-47.0] vs 21.0 [9.0-40.0]; $p < 0.01$). The median CCI was 2.0 (0.0-7.0) for survivors and 3.0 (1.0-10.0) for non-survivors. The CCI of non-survivors was significantly higher than that of survivors ($p = 0.005$). All these parameters and the relationships with mortality are shown in Table 3. The mortality rate of patients with CCI > 3 was significantly higher than patients with CCI ≤ 3 (55.1% vs 35.7%; $p < 0.05$) (Table 4).

Multiple logistic regression analysis was applied to the APACHE II score, age and CCI, and the APACHE II and CCI were left on the model with a value of $p < 0.491$. According to the result of this analysis, the odds ratio of APACHE II score for mortality was found to be 1.214 (95% Confidence Interval: 1.154-1.276), and the odds ratio of CCI for mortality was found to be 1.320 (95% Confidence Interval: 1.088-1.602).

When the relationship between the APACHE II, CCI and LOS was analysed, there was a significant positive correlation between APACHE II and LOS ($r = 0.314$; $p < 0.001$). CCI was found to be positively

related with LOS ($r = 0.147$; $p = 0.020$). There was no significant relationship between CCI and APACHE II ($p > 0.05$). The relationships between the parameters are shown in Table 5.

DISCUSSION

Many studies have examined the factors affecting mortality and the risk scoring methods in intensive care patients. Although there are several scoring

Table 2. Demographic characteristics of all patients (n = 251)

Age (years)	78.79 ± 6.70
Gender	
Male	109 (43.4%)
Female	142 (56.6%)
APACHE II score	26.0 (9.0-47.0)
CCI	2.0 (0.0-10.0)
Length of stay (days)	10.06 ± 8.60
Final status	
Survivors	148 (59.0%)
Non-survivors	103 (41.0%)

APACHE = Acute Physiology and Chronic Health Evaluation, CCI = Charlson Comorbidity Index

Table 3. APACHE II score and comorbidity index and their relationship with mortality

Parameters	Survivors (n = 148) Median (range)	Non-survivors (n = 103) Median (range)	<i>p value</i>
Age	79.5 (65.0-99.0)	80.0 (65.0-93.0)	0.975
APACHE II score	21.0 (9.0-40.0)	31.0 (13.0-47.0)	< 0.001
CCI	2.0 (0.0-7.0)	3.0 (1.0-10.0)	0.005

APACHE: Acute Physiology and Chronic Health Evaluation, CCI: Charlson Comorbidity Index

systems, the APACHE II score is still one of the most frequently used risk scoring systems and it has high success rates for the prediction of mortality [1]. In the current study, the APACHE II score was determined to have a significantly positive correlation with both mortality and LOS, as expected. In a prospective study of 109 patients admitted to the ICU for 1 year, malnutrition, delirium, and APACHE II were found to be risk factors for long-term mortality [8].

Recently, the mean age of patients admitted to ICU has been increasing [2, 9]. Aging itself is considered to be the most important risk factor for several chronic conditions [10]. In two studies of elderly patients, age itself was not found to be an independent risk factor for mortality [8, 11]. In only

one study, mortality was significantly associated with age in univariate analysis but not in multivariate analysis [12].

In the current study, the mean age of the patients was 78.79 ± 6.70 years and similar to previous results, it was demonstrated that age is not a risk factor for mortality and LOS in older patients. As APACHE II was the already known predictive score and age was shown not to be related with mortality and LOS, then the comorbidity status becomes very important. For elderly patients, there is no generally valuable and validated index for comorbidity which can predict prognosis especially in intensive care.

The Charlson comorbidity index (CCI) is the most extensively studied comorbidity index for predicting

Table 4. The relationship between CCI and mortality

	Survivors n (%)	Non-survivors n (%)	<i>p value</i>
Patients with CCI ≤ 3	117 (64.3%)	65 (35.7%)	< 0.05
Patients with CCI >3	31 (44.9%)	38 (55.1%)	
Total	148 (59.0%)	103 (41.0%)	

CCI: Charlson Comorbidity Index

Table 5. The relationship between CCI, APACHE II score and length of stay

(n = 251)		LOS	APACHE II	CCI
LOS	r	1.000	0.314	0.147
	<i>p</i>	-	< 0.001	0.020
APACHE II	r	#	1.000	0.108
	<i>p</i>		-	0.087
CCI	r	#	#	1.000
	<i>p</i>			-

APACHE = Acute Physiology and Chronic Health Evaluation, CCI = Charlson Comorbidity Index, LOS = Length of stay

mortality. It includes the number and severity of comorbid conditions [5]. The CCI has been shown to be important and effective prognostic marker for mortality in many diseases and conditions [6, 7], although the number of studies on critically ill elderly patients is limited. In a study of elderly patients admitted to ICU, age, critical illness, cardiopulmonary resuscitation, and the need for mechanical ventilation and/or vasopressor therapy were found to be independent risk factors associated with adverse outcomes [2]. In the current study, the CCI of non-survivors was found to be significantly higher than that of survivors and the OR was 1.320 for mortality. Therefore, this finding supports the view that CCI is a valuable index for critically ill elderly patients. Similar to the current study, Buntinx *et al.* [13] showed that the CCI is a predictor of short-term mortality and hospitalization in a large cohort of 2,624 institutionalized elderly people. In contrast, in a prospective study with 444 elderly patients, a comparison was made of the abilities of six different validated comorbidity indices including CCI, to predict mortality, LOS and institutionalization in a geriatric hospital. The results showed that the geriatrics index of comorbidity (GIC) was the most accurate predictor of mortality during hospitalization rather than CCI [12]. In contrast, the results of the current study demonstrated that both APACHE II and CCI have a significant impact on LOS. There was no relationship between CCI and APACHE II. Therefore it can be suggested that CCI be used as a prognostic marker for LOS in addition to APACHE II.

Quach *et al.* [14] prospectively compared the discriminative ability of the CCI to the APACHE II in predicting hospital mortality in adult multisystem ICU patients. They found that CCI is a poor predictor of mortality and does not perform as well as the APACHE II in predicting hospital mortality in ICU patients. However, they suggested that CCI can be considered as an alternative method of risk assessment when illness scores are unavailable or are not recorded in a standard way. Since the CCI includes comorbidities which are usually seen in older ages, one of the reasons for their result maybe that they included patients > 17 years with a median age of 56. In our study, we only included geriatric patients (age > 65 years) which are expected to have chronic comorbidities before ICU administration. In a

prospective cohort study of 201 ICU patients, the CCI was found to be useful to discriminate between survivors and nonsurvivors [15]. They also found that APACHE II system was an excellent predictor. (area = 0.87, SE = 0.04). They suggested that CCI could improve prognostic predictions even for critically ill patients. Although they included all patients without age discrimination, they found a significant result for CCI similar to our result.

Limitations

Limitation of the current study was its retrospective design and heterogenous patient selection. Else, the quality of comorbidity data in retrospective review of medical records or administrative data may be unclear and under-report true incidence. Therefore prospective studies are needed.

CONCLUSION

Many parameters are used to predict prognosis in ICU patients. The results of the current study revealed that the mortality rates were significantly higher in patients with higher APACHE II scores. The CCI was higher in the non-survivor group and was strongly associated with mortality and LOS in critically ill older patients. Due to its easily available nature, it is appropriate to use it as a prognostic index in critically ill elderly patients.

Conflict of interest

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Chondroid metaplasia: a rare subtype of metaplastic breast carcinoma

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ABSTRACT

Metaplastic breast carcinoma (MBC) is a subtype of breast malignant lesions which is very rare seen. Clinically, MBC is more aggressive and has worse prognosis than other subtypes of breast cancers. A 61-year-old female patient who had a rapidly enlarging and palpable mass on the left breast applied. Core biopsy was performed and pathology was reported as invasive ductal carcinoma. The patient who had been diagnosed with breast cancer was operated and postoperative course was unremarkable. She was discharged postoperative third day with no complication. Postoperative specimen pathology was reported as a rare type of breast metaplastic carcinoma which was chondroid metaplasia. Here we aimed to report, a case of chondroid metaplasia which is a rare type of metaplastic breast carcinoma with the literature.

Keywords: Metaplastic carcinoma, chondroid metaplasia, breast cancer

Metaplastic breast carcinoma is rare seen among the breast malignant lesions [1]. 1-2% of malignant breast lesions was determined as MBC [2, 3]. Metaplastic breast carcinoma has both epithelial and mesenchymal malignant tissue components. According to the components they contain, metaplastic breast carcinoma has five subtypes. According to the 2012 WHO classification; low grade adenosquamous carcinoma, fibromatous-like metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma, mesenchymal differentiation carcinoma (chondroid differentiation, osseous differentiation and other mesenchymal differentiation types) [4]. Clinically, MBC is more aggressive and had a shorter overall survival than other subtypes of breast malignancies. MBC had a worse prognosis due to present with a larger tumor size which were mostly undifferentiated type and involvement of less lymph nodes, which are usually

triple negative [3-5]. Although the management of MBC was essentially similar to invasive ductal carcinoma, there is no specific treatment approach for MBC management [3, 6, 7].

CASE PRESENTATION

A 61-year-old female patient presented with a complaint of a rapidly growing, painless mass on the left breast, covering almost all of the breast. Breast ultrasonography showed a 6x6 cm solid lobular contoured lesion with heterogeneous calcifications and acoustic shade which located in left breast lower middle zone. In thorax computed tomographic imaging, in the left breast there was a 63x55 mm irregular contoured mass containing calcifications, and thickening of the breast skin and subcutaneous tissues

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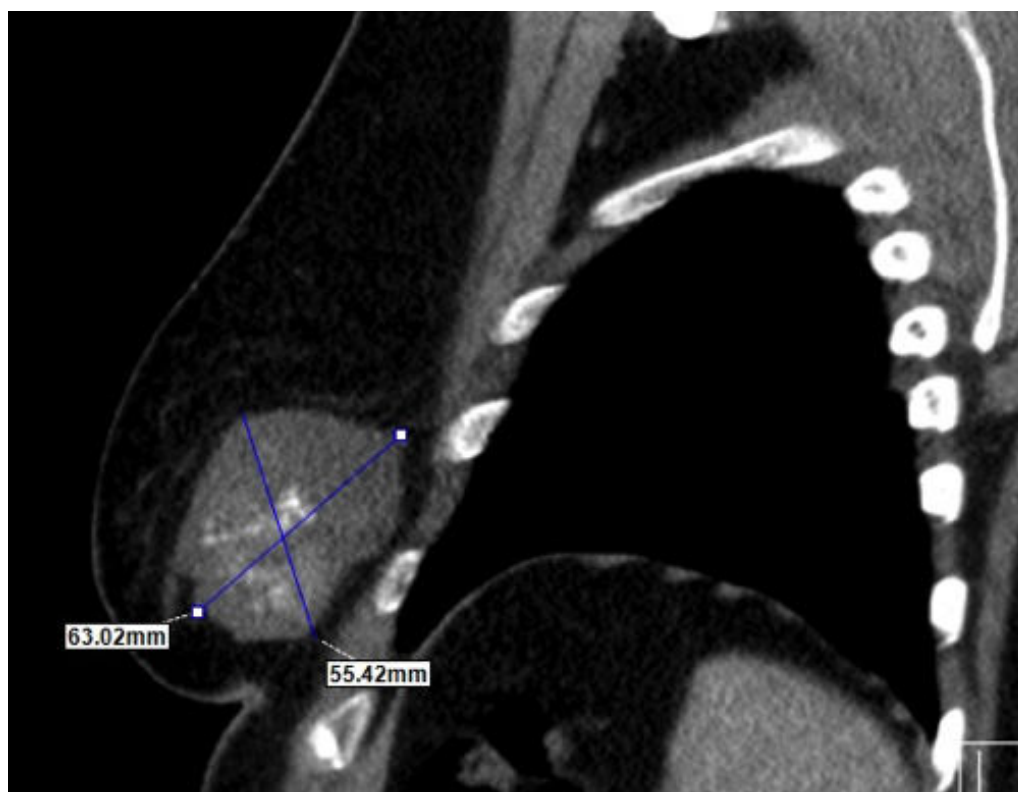


Fig. 1. Thorax CT imaging shows a 63×55 mm irregular contoured mass containing calcifications, and thickening of the breast skin and subcutaneous tissues in the left breast.

(Fig. 1). Core biopsy was performed. Pathology showed invasive ductal carcinoma with ER 40% (+), PR (-), Ki67: 20%, CerB2: (-), E-cadherin: (+). No distant metastases were observed in the preoperative imaging methods. Written informed consent form was obtained for patient treatment, surgery and publication. Peroperative sentinel lymph node biopsy (SLNB) was performed. Axillary dissection was not performed upon arrival as a frozen of SLNB reported as reactive lymphadenopathy. Left mastectomy was performed because of mass that covers almost all of the breast. Postoperative course was unremarkable. Postoperative third day, hemovac dren was taken and she was discharged with no complication. Postoperative specimen pathology was compatible with a rare subtype of metaplastic breast carcinoma, as chondroid metaplasia. The histopathological examination showed; ER 40% (+), PR 20% (+), Ki67: 40%, CerB2: (-), E-cadherin: (+) with a size of 6×5×4cm tumor which located lower middle zone of breast, with free tumor on surgical margin.

The patient was referred to the department of medical oncology further postoperative treatment.

Patient receiving adjuvant chemotherapy, without recurrence at postoperative 25th month are followed.

DISCUSSION

Metaplastic breast carcinoma which has epithelial and mesenchymal malignant tissue components, is generally presented rapidly growing masses. MBC is aggressive, generally had a poor prognosis and had a high grade, with a propensity for recurrence [2, 3]. Preoperative radiological findings has similarity to other malign breast lesions. Radiological findings may be varied according to tumor components [3]. MBC is mostly seen in the fifth decades, and generally come up with fast-growing large-sized masses in short time intervals [2]. It has been determined that the tumor size can be changed in the range of 1.4-14.8 cm with the studies [3, 8].

In the majority of studies performed, it was found that hormone receptors, which is another factor that affects the treatment of metaplastic breast cancer, are negative [2, 3, 6]. Due to that, hormonal therapy

largely has no role in these patients with MBC. Cimino-Mathews *et al.* [8] found 20% ER/PR positive, 9% HER-2 positive, and 69% triple negative in their study which involving 45 patients with metastatic breast carcinoma. Despite the large size of tumors in MBC lymph node involvement is less seen than adenocarcinoma [3, 5, 6]. The incidence of lymph node metastasis can be change between 0-63% [5]. When patients diagnosed with MBC disease stage generally tends to be higher in stage than in invasive carcinoma and also prognosis of metaplastic carcinoma is worse than invasive carcinoma [6]. Important in determining the prognosis is the type and prevalence of the metaplastic component such as tumors with sarcomatous component have been reported to have a worse prognosis. [7]. However, 5-year survival rate reported with metaplastic carcinoma chondroid or osseous metaplasia is 20-68% and also 19-25% axillary lymph node metastasis, 21% distant metastasis [4]. Optimal treatment strategies for metaplastic breast cancer are still unclear. There is no standard adjuvant therapy for MBC. Chemotherapy shows lower response rates than other basal-like tumors in MBC which generally has negative for estrogen receptor, progesterone receptor and HER-2 negative [3]. However, the neoadjuvant chemotherapy (NAC) for MBC is not well defined, we know that the role of NAC has expanded from its use in inflammatory and locally advanced tumors to patients with early stage breast cancer. Al Hilli *et al* [9] reported that MBC had a poorly responsive to NAC. However, Tseng and Martinez [10] and PaulWright *et al.* [11] suggested that administration of radiotherapy is associated to improved survival in MBC.

MBC with presenting fast grow lump, studies suggesting mastectomy or modified radical mastectomy (MRM) rather than lumpectomy [3, 6, 7]. However, there are publications showing no contribution to survival for breast conserving surgery or mastectomy [3, 10]. MRM or mastectomy is preferable to in breast conservation surgery (BCS); because of the possibility of local recurrence between 35-62% within the first 2-5 years [12].

CONCLUSION

MBC breast carcinoma is a rare seen type of breast

cancer which presented with rapidly growing palpable masses, although the rate of lymph node metastasis is low. Because of the higher risk of local recurrence in MBC, MRM or mastectomy is generally preferred to BCS for surgical treatment. Considering poor prognosis and decreased response to treatment for MBC, new treatment modalities should be identified.

Informed consent

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

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Congenital adrenal hyperplasia with an ovarian adrenal rest tumor: a case report

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ABSTRACT

Adrenal rest tumors (ART) are extra-adrenal findings of adrenal tissue. Testicular adrenal rest tumors (TART) are widespread in males with congenital adrenal hyperplasia (CAH). Ovarian adrenal rest tumours (OART), which form in females with CAH, are less commonly seen. Reports in literature of OART are extremely rare. The case is here presented of a 43-year-old female who was diagnosed at the age of 15 years with CAH and underwent bilateral adrenalectomy at the age of 37. On presentation at our clinic, 4×2 cm mass was determined on the right adnexa in the advanced tests and a right-side salpingo-oophorectomy was performed. The pathology examination reported heterotopic adrenal cortical tissue. Routine ovarian imaging in females with CAH is not indicated. Although OART are rarely seen, they should be kept in mind and these patients should be evaluated radiologically together with laboratory tests.

Keywords: Ovarian adrenal rest tumor, congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is a group of adrenal steroid synthesis disorder disease, which emerges as a result of a deficiency of one of the enzymes in the steroid synthesis pathway. More than 90% of patients are deficient in 21-hydroxylase enzyme (21OHD). A deficiency of 11-beta hydroxylase enzyme is seen in 5%-8% of CAH patients and is the second most common type. The disease has autosomal recessive transfer. Steroid synthesis is decreased in these patients and as a result, the adrenocorticotropic hormone (ACTH) level increases, leading to proliferation of all cells with adrenal cortex origin [1]. The clinical results are over-production of adrenal androgens with the accumulation of precursor hormones and hypertrophy of the adrenal glands [2, 3]. By deviating from the androgen biosynthesis path, these precursors

lead to virilisation in female fetuses or infants and with accelerated skeletal maturation in both males and females, cause rapid postnatal growth, early puberty and short adult height. While males with classic CAH do not show any abnormalities at birth, females are born with ambiguous genitalia [4].

ARTs are extra-adrenal findings of adrenal tissue and there is an ART in 50% of newborns with CAH. ARTs are gradually covered and prevalence falls to 1% in adulthood [5]. TART are widespread in males with CAH, with a high prevalence of 95% reported in some studies and they can be determined at the onset of childhood [6]. TART is a benign tumour, seen bilaterally in the majority of cases [2]. OART, which form in females with CAH, are less commonly seen and are another extra-adrenal tissue [7]. Besides

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TARTs, adrenal rests may develop elsewhere in the retroperitoneum, including the ovaries and surrounding structures. OART appear to be uncommon in women with classic 21OHD, with none found in a systematic evaluation of 13 women [8] and only scattered cases reported in the literature [9]. The etiology appears related to sustained elevations in ACTH as a re-

sult of poor compliance, as in men with TART. It is not known if glucocorticoid or mineralocorticoid therapy reduces adrenal rest development and/or size.

Reports in literature of OART are extremely rare. The case is here presented of a female diagnosed at the age of 15 years with CAH who underwent bilateral adrenalectomy at the age of 37 and on presentation at

Table 1. Laboratory test results

	Result	The reference range
Na	146 mEq/L	135-150 mEq/L
K	4.9 mEq/L	3.5-5.5 mEq/L
BUN	20.6 mg/dl	5-20 mg/dl
Creatinine	1.25 mg/dl	0.5-1.4 mg/dl
Ca	9.09 mg/dl	8.5-10.5 mg/dl
P	2.71 mg/dl	2.7-4.5 mg/dl
ALT	12 U/L	20-40 U/L
AST	18 U/L	7-39 U/L
Glucose	89 mg/dl	70-110 mg/dl
Hemoglobin	13 gr/dl	12-14 gr/dl
Prolactin	22.63 ng/ml	4.79-23.3 ng/ml
FSH	3.66 mIU/ml	3.5-12.5 mIU/ml
LH	13.46 mIU/ml	2.4-12.6 mIU/ml
TSH	0.70 uIU/ml	0.27-4.2 uIU/ml
FT4	1.18 ng/dl	0.93-1.7 ng/dl
FT3	3.62 pg/ml	2-4.4 pg/ml
17 OH-PG	4.57 ng/ml	0.59-3.44 ng/ml
Total testosterone	256 ng/dl	8-50 ng/dl
Free testosterone	4.08 pg/ml	0.45-3.17 pg/ml
Estradiol	147 pg/ml	12.5-166 pg/ml
ACTH	> 2000 pg/ml	7.2-63.3 pg/ml
Cortisol	0.895 ug/dl	6.2-19.4 ug/dl

Na = sodium, K = potassium, BUN = blood urea nitrogen, Ca = calcium, P = phosphate, ALT = alanine aminotransferase, AST = aspartate aminotransferase, FSH = follicle-stimulating hormone, LH = luteinizing hormone, TSH = thyroid-stimulating hormone, FT4 = free thyroxine, FT3 = free triiodothyronine, 17 OH-PG = 17 hydroxyprogesterone, ACTH = adrenocorticotropic hormone

the age of 43 years, was determined with ART on the right ovary.

CASE PRESENTATION

A 43-year-old female presented at our clinic for gender re-assignment. It was learned from the patient history that from tests applied at age 15, because of absence of menarche and increased facial and chest hair, a diagnosis was made of CAH due to 21OHD enzyme deficiency. In the karyotype analysis, 46XX was determined. Treatment was started for the patient but the patient did not take the medication regularly or attend follow-up examinations. At the age of 37, the patient was hospitalized because of nausea, vomiting and abdominal pain. Acute renal failure was diagnosed and hemodialysis was applied. On the dynamic surrenal computed tomography (CT) examination, lobular, contoured, heterogenous structures were seen of approximately 5×5×6 cm in size in a right suprarenal localisation and of approximately 12×8×17 cm in size in the left suprarenal location. These mass lesions were pushing both kidneys towards the inferior, in the medulla of both kidneys there were millimetric calcifications and dense soft tissue 1.5×1 cm was determined in the left ovary. The mass lesion identified by the radiology department may be bilateral surrenal hyperplasia with malignant transformation. Because of the tumor was thought to

be bilateral adrenal hyperplasia with malignant transformation and the mass size was large and pressure to the kidney was applied, the patient had undergone bilateral surrenalectomy operation. The pathology examination was reported ascortical medullar adrenal hyperplasia containing widespread myelipomatous foci with positive vimentin and chromogranin staining. Treatment of hydrocortisone and fludrocortisone was started. After 2 weeks of hemodialysis treatment, the patient's kidney function was returned to normal.

In the physical examination at presentation, blood pressure was 110/80 mmHg, pulse: 90 beat per minute, respiration: 20/minute. The external appearance was male phenotype. There was widespread hyperpigmentation on the skin. There was male-type hair on the chest, face and the pubis. Breast development was tanner stage 2. Other system examinations were normal. Laboratory test results at presentation were defined in Table 1.

On the abdominal ultrasonography (USG), there was an appearance of a heterogenous hyperechoic mass 48×28×32 mm in size, laterally adjacent to the uterus on the right side. On abdominal-pelvic CT, neither of the adrenal glands were observed. At the level of both adnexa, a hyperdense, nodular lesion approximately 2 cm in diameter was reported and at the level of the right adnexa, a hypodense area 4×2 cm extending to the Douglas pouch. A right-side salpingo-oophorectomy was applied to the patient. Heterotopic

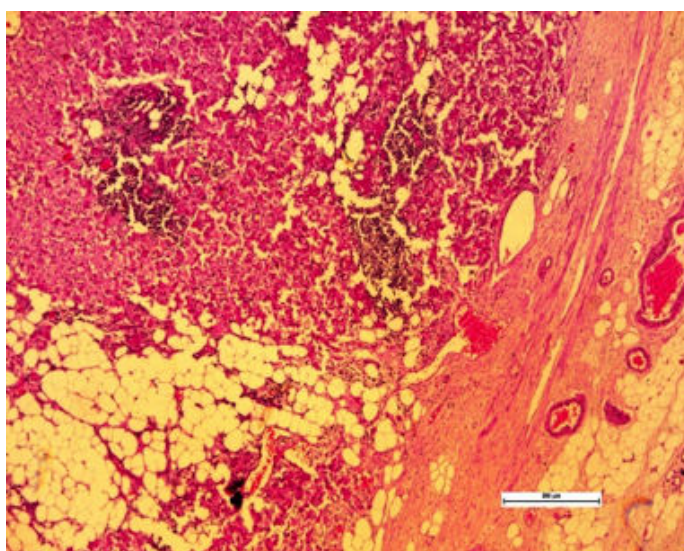


Fig. 1. Lesion with regular border separate from the tissue surrounding the ovary

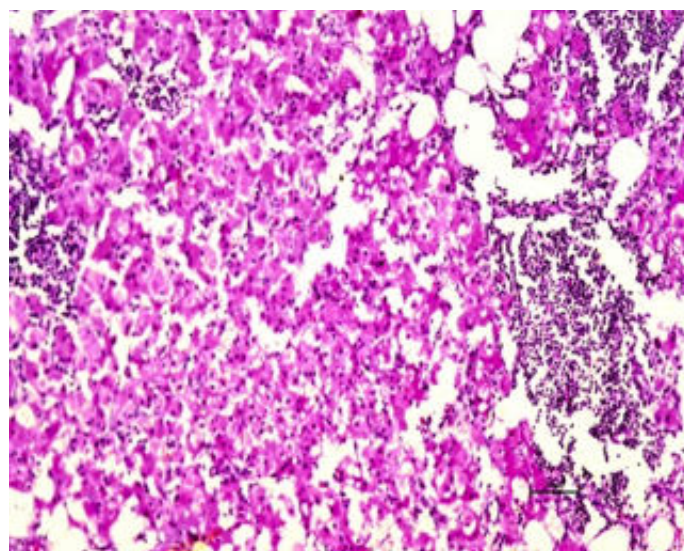


Fig. 2. Inflamed cells and mature adipocytes around heterotopic adrenal cortical cells (H&E ×10)

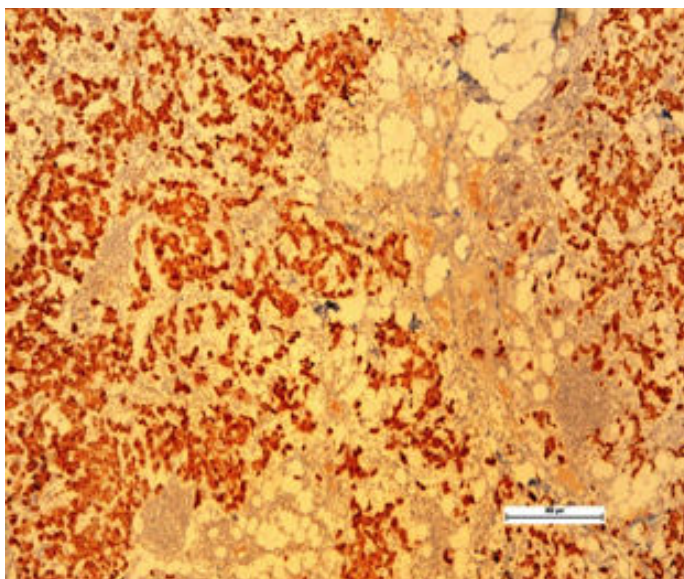


Fig. 3. Positive reaction with inhibin in heterotopic adrenal tissue.

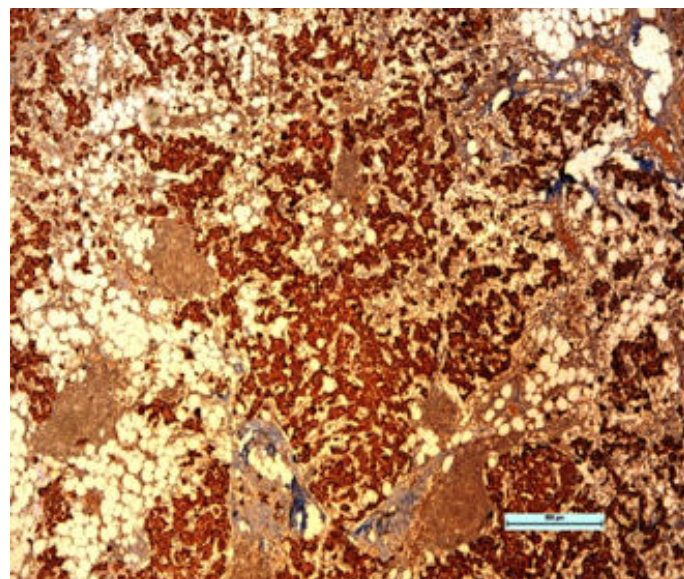


Fig. 4. Positive reaction with melen A in heterotopic adrenal tissue

adrenal cortical tissue was reported in the pathology examination. The immunohistochemical test results were determined as melen A: diffuse positive, inhibin: diffuse positive, vimentin: focal mild positive, synaptofizin negative, chromogranin: negative, CD68: negative, CD10 negative, and 1% of proliferative index with Ki 67 (Figures 1, 2, 3, 4, and 5)

In the postoperative period, because of the patient referred to another center, she could not be followed-up.

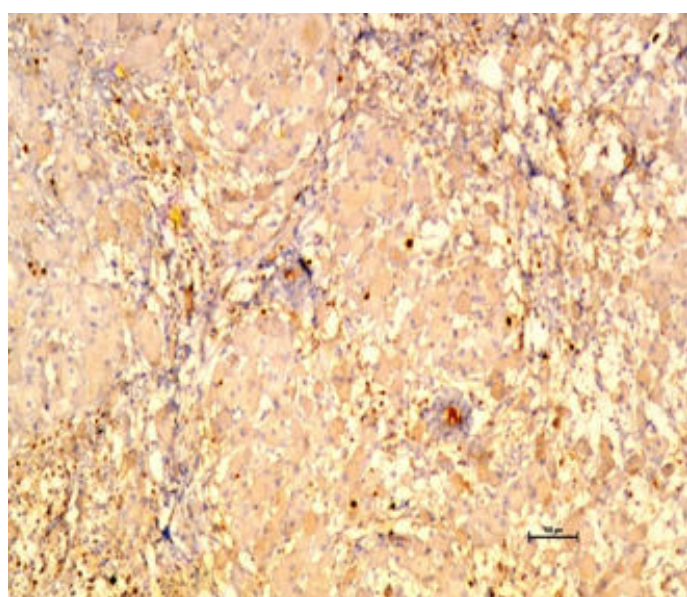


Fig. 5. 1% proliferative index with Ki 67 in heterotopic adrenal tissue (Ki67 ×10)

DISCUSSION

In comparison with the high incidence rate of TART, the very low incidence rate of OART in female ovaries raises questions about the mechanisms preventing the development of OART. Val *et al.* [10] reported that TART develops from adrenal gland cells that have migrated to the testis or from local steroidogenic stem cells [10]. These cells express MC2R which is the ACTH receptor regulating Shh expression related to adrenal development and differentiation [11]. The first question to be addressed is whether or not there is similar migration of adrenal-like cells in the ovaries. In inguinal-scrotal operations in male children, incidental findings have provided evidence of the migration of primordial adrenal cell cortex cells together with coelomic epithelial cells [12, 13]. These findings show that the difference between males and females in the incidence of adrenal rest tumours could be associated not with abnormal adrenal tissue migration but with the differences in ontogenesis of the gonads.

Wnt4 is one of the main transcription factors of ontogenesis in the ovaries. This factor suppresses endothelial and steroidogenic cell migration in the developing XX gonad and prevents both male-specific coelomic blood vessel formation and the production of ectopic steroids including steroidogenic CYP17A1 and HSB3B2 enzymes [14]. Functional studies have

reported that mutations of Wnt4 do not suppress the synthesis of the androgen synthesis enzymes CYP17A1 and HSB3B2 in the human ovaries. Females with a mutation in Wnt4 have increased steroidogenic enzymes and testosterone synthesis [15]. The presence of Wnt4 in the ovaries and the absence of testes could explain the difference in adrenal tumour incidence between males and females.

In a systematic review by Tiosano *et al.* [9] in 2010, only 10 OART cases were reported. For the clinician, the severity of the OART must not be underestimated as misdiagnosis can be deadly [7]. However, prompt diagnosis of OART can be elusive. This raises the concern of the lack of defined criteria for a radiologic diagnosis of OART. The sensitivity of USG and magnetic resonance imaging (MRI) for detecting small ovarian rest tumors is not known, and other androgen-producing tumors of the ovary often are not found with conventional imaging studies. Thus, the true prevalence may be higher, as most tumors have been identified during surgery or at autopsy. Rest tumors occur primarily in the ovarian tissue and, less often, in the paraovarian/adnexal area [9]. Concerns have emerged related to deficiencies in the criteria defined for the radiological diagnosis of OART. Routine ovary imaging is not indicated in females with CAH. However, when there is ovary dysfunction, ovarian radiological imaging is recommended, first with USG for the determination of OART or polycystic ovaries. Using ultrasonography and MRI, Stikkelbroeck *et al.* [8] attempted to establish radiologic criteria for establishing a diagnosis of OART in 13 females with CAH. However, there were no cases of OART, a testament to the low prevalence of the tumour. This is in contrast to TART where MRI and ultrasound, the preferred diagnostic modalities, readily diagnose the disease, even tumours several millimeters in diameter [16]. In a study in the USA in 2012, with cosyntropin stimulus of 18F marked fluoro-2-deoxy-d-glucose positron emission tomography/ computed tomography scanning, correct identification was shown of adrenal rest tissue that could not be seen with conventional imaging in CAH patients following adrenalectomy. Thus, it was reported that it was possible to define successful surgical resection [17]. While unfamiliarity with the diagnosis of OART may lead to surgical treatment that may not be necessary, the large size of

the tumour coupled with lack of outcome data may justify removal in some instances. With the advancement in our understanding of how OART present and the natural history of these benign tumours, the possibility arises that organ-sparing protocols can be developed, similar to the treatment of TART [18].

CONCLUSION

In our case, there was adrenal steroid synthesis following bilateral adrenalectomy. Ectopic adrenal rest tissue can cause clinical symptoms. Firstly, ectopic adrenal cells can be hormonally active and can undertake pathological steroid production in CAH patients. This may cause increased adrenal steroid levels postoperatively in adrenalectomy patients in particular. Secondly, there may be malignant degeneration of adrenal rest tissue. However, there is no information available in the literature. Surgical treatment for OART remains unclear due to the rarity of these tumours. For girls and women with CAH for whom medical treatment is unavailable or who are noncompliant with their therapy, OART should be considered when ovarian masses are detected. If an OART is detected early enough and glucocorticoid therapy is received, it is possible that the OART will decrease in size following suppression of ACTH levels. There is a need for further studies to determine whether regular screening is of benefit or not for these tumours.

Informed consent

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

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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A practical method in measurement of perforation size during cartilage tympanoplasty

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ABSTRACT

Cartilage has been used in otologic surgery for ossicular reconstruction and grafting since 1960s. Due to low metabolic rate, stiffness and stability properties with regard to fascia, it is thought to be more effective in tympanoplasty. With the help of this measurement technique, redundant oversized harvesting of cartilage can be prevented and overmanuplation during graft replacement especially after a delicate ossiculoplasty procedure can be avoided. The aim of this study was to demonstrate the preparation of optimal island cartilage composite graft with a simple sterile suture package template for the appropriate size of the tympanic membrane perforation, and to provide a functional surgery with minimal donor site defect and minimal manipulation. With this technique, 143 patients with chronic otitis have been operated in our clinic. No complications with respect to this method, have been observed up to date. Using an easily prepared template is a simple and effective method for measuring the perforation size.

Keywords: Cartilage, tympanoplasty, perforation size measurement, endoscopic cartilage tympanoplasty, butterfly inlay myringoplasty

Cartilage usage as a graft in tympanoplasty has become more popular after the first attempt by Salen since 1963 [1]. Tragal and conchal cartilage are the preferred donor sites due to easy of access in the surgical field [2]. Different types of cartilage modifications were tried and Tos [1] proposed a classification of cartilage tympanoplasty methods which was classified in 7 groups (Group A to F).

Composite island, shield and butterfly cartilage grafts are the commonly used graft types especially in pars tensa perforations [3, 4]. Due to individual anatomic variations of annular ring size, tympanomeatal angle and perforation shape, localization; surgeon may have some trouble to predict the optimum size of the cartilage graft. A trial of improper, oversized graft replacement especially after a delicate

ossiculoplasty may result in over manipulation which can result in disruption of ossiculoplasty and prolongation of the surgery. Moreover, insufficient cartilage graft may lead to dehiscence between perforation edge and perforation margin [2].

The aim of this study was to demonstrate the preparation of optimal island cartilage composite graft and butterfly graft with a simple template for the appropriate size of the tympanic membrane perforation, and to provide a functional surgery with minimal donor site defect and minimal manipulation.

TECHNIQUE

A sterile suture package was cut and prepared as

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template (Fig. 1). Before the elevation of tympanomeatal flap, the size of the perforation after refreshment of the perforation edges was confirmed whether it was adequate or not, by fitting the paper template over the perforation site. After the determination of optimum size of island cartilage graft, harvesting of the tragal cartilage was performed according to measured size of template. Before the end of surgery, after performing the ossiculoplasty, optimum closure of perforation was rechecked with the template after reposition of tympanomeatal flap. Finally, closure of the tympanic membrane was completed with this preformed cartilage graft. This technique was used in 143 tympanoplasty surgeries with endoscopic and microscopic approaches and no complications such as chorda tympani, ossicular chain or tympanomeatal flap damage with respect to this method have been observed up to date. (Figs. 2, 3 and 4).

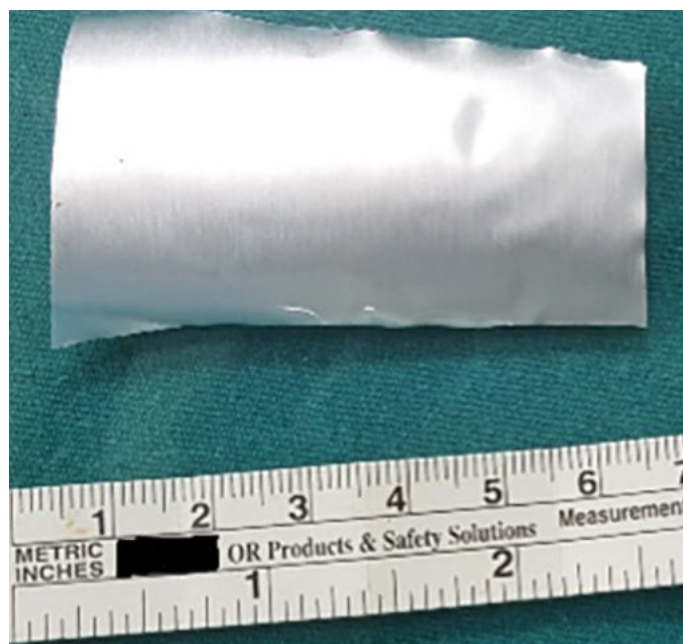


Fig. 1. Sterile suture paper

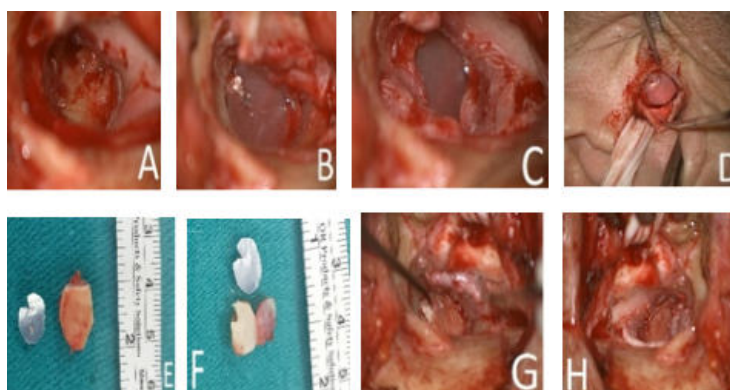


Fig. 2. Suture paper template technique in microscopic tympanoplasty. (A) Microscopic view of perforation after refreshment of the edges, (B) Suture paper template demo after tympanomeatal flap elevation, (C) Template fitting after reposition of tympanomeatal flap, (D) Harvest of tragal cartilage according to template, (E, F) Cartilage graft shaping, (G) Cartilage graft replacement before tympanomeatal flap reposition, and (H) Cartilage graft replacement after tympanomeatal flap reposition.

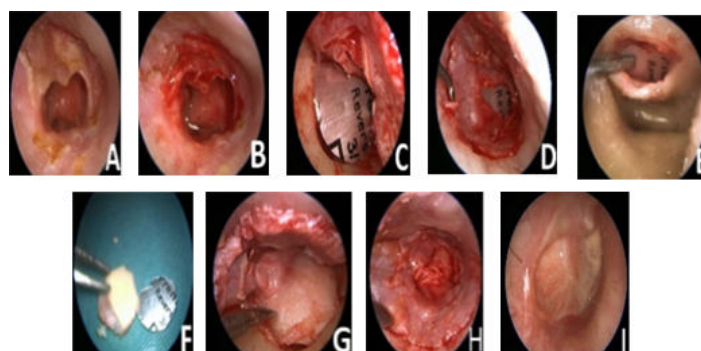


Fig. 3. Suture paper template technique in endoscopic transcanal tympanoplasty. (A) Endoscopic view of perforation, (B) After refreshment of perforation edges, (C) Suture paper template demo after tympanomeatal flap elevation, (D) Template fitting after reposition of tympanomeatal flap, (E) Harvest of tragal cartilage according to template, (F) Cartilage graft shaping, (G, H) Cartilage grafting after tympanomeatal flap reposition, and (I) Postoperative 6. month view of tympanic membrane.

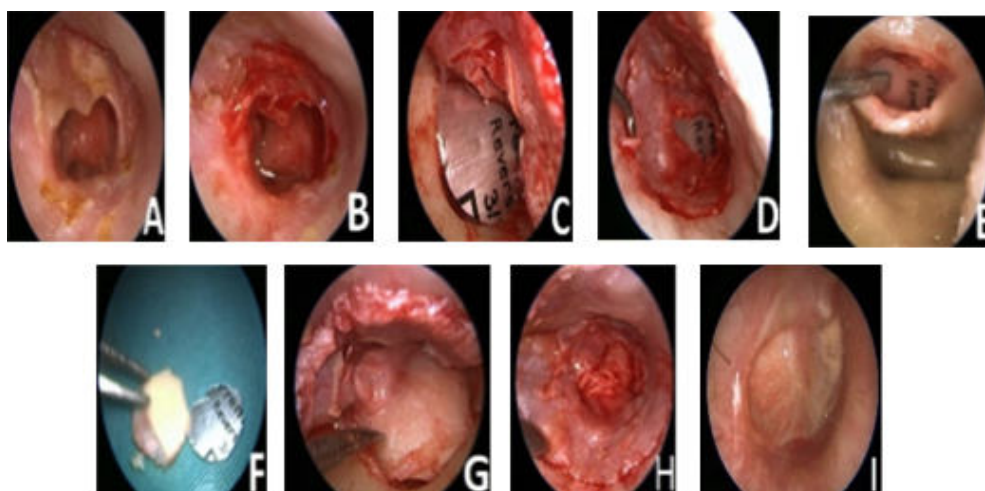


Fig. 3. Suture paper template technique in endoscopic transcanal tympanoplasty. (A) Endoscopic view of perforation, (B) After refreshment of perforation edges, (C) Suture paper template demo after tympanomeatal flap elevation, (D) Template fitting after reposition of tympanomeatal flap, (E) Harvest of tragal cartilage according to template, (F) Cartilage graft shaping, (G, H) Cartilage grafting after tympanomeatal flap reposition, and (I) Postoperative 6. month view of tympanic membrane.

DISCUSSION

Cartilage has been used in otologic surgery for ossicular reconstruction and grafting since 1960s. Due to low resorption rate, stiffness and stability properties with regard to fascia, it is thought to be more effective in patients especially with higher risk of reperforation. There is a still debate about the thickness of the cartilage which influences the hearing outcome [5]. However, to get hearing success, anatomic closure of perforation must be obtained firstly. Thus, optimum size and shape of cartilage graft with proper replacement is needed. Seta *et al.* used auricular speculum to evaluate the required graft size to reduce the surgical time during cartilage tympanoplasty [6]. Also Eren *et al.* [7] introduced a device called ‘otologic compass’ to measure the perforation size during inlay butterfly myringoplasty. They concluded that this device decreased the number of cartilage shaping attempts and operation time. By the help of this template technique exact fitting of graft can be demonstrated especially at the anterior border of the perforation and optimum relationship of graft with bony annulus can be achieved. At the donor site of graft, this template provides sufficient amount of cartilage harvest, preventing excessive cartilage loss which can result in better cosmetic outcome. Moreover, there is no need for any extra device thus, using a suture paper is cost effective.

CONCLUSION

Using an easily prepared template is a simple and effective method for measuring the perforation size. With this method, sufficient harvesting can be achieved and overmanipulation of graft during placement can be avoided which can shorten the duration of the surgery.

Conflict of interest

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