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TABLE OF CONTENTS

Archives of Current Medical Research
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EDITORIAL

Hasan Serdar Öztürk, M.D., Ph.D.
Editor in Chief

Getting Started...

As we are setting sail as a new scientific journal encompassing all fields of medicine, dentistry and related fields, we are very eager to contribute to the current literature. Our journey started with a spark of ideas coming from our younger, ambitious colleagues. We have put together a multidisciplinary experienced team of editors, held many meetings in order to pin all the ideas down and put everything on track. Our main objectives are to preserve the quality of the journal and the articles published, to publish valuable articles that may be a significant contribution to the current literature and eventually become one of the top journals in this scope. In the long run, we wish to be accepted into internationally recognized indexes.

As an open-access e-journal, Archives of Current Medical Research is a journal that meets the necessities of the Information Age. It is easy to access, open to sharing information without any limitation of time or place and we work hard as a team to carry out a fast article processing period. We believe this first issue will be the beginning of many to come. We know there is a long road ahead of us and we all feel more than ready to work harder and meticulously with each issue.

I would like to thank the originators of the journal for their idea, ambition and effort, our team of editors and reviewers for all their contributions, and also all authors who have provided valuable scientific data to this very first issue of Archives of Current Medical Research. With our hearts and minds set on knowledge, success and qualified research; we are keen to witness and together realize the whole potential of the editorial and reviewer team and unfalteringly reach our goals in the future with the help of every researcher who wishes to contribute.

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REVIEW ARTICLE

Approach to Obesity in Childhood

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Abstract

Childhood obesity prevalence is increasing worldwide. The most common cause of obesity in children is a positive energy balance due to excess caloric intake in contrast to caloric expenditure combined with a genetic predisposition for weight gain. Obesity causes type 2 diabetes mellitus, hypertension, cardiovascular diseases, osteoporosis and some cancers. There is limited information on the efficacy and safety of medications for weight loss in children. In this paper, definition, etiopathogenesis, differential diagnosis, co-morbidities, and treatment of obesity in children will be reviewed.

Key words: Obesity, Childhood, Adolescence, Pediatric, Overweight.

DEFINITION AND FREQUENCY

Obesity is a chronic disease that develops with the increase in body fat mass as a result of higher amount of energy intake compared to the amount of energy spent. Obesity refers to excessive fat accumulation. Obesity is considered as one of the 10 most dangerous diseases by the World Health Organization, and it may affect all endocrine, metabolic, cardiovascular and respiratory systems of the body and cause a wide variety of problems and death (1-4).

Childhood obesity is a rising global health problem. The number of overweight and obese children in the 0-4 age group increased from 32 million in 1990 to 41 million in 2016 throughout the world. The number of overweight and obese children in the world is expected to reach 70 million by 2025, if the current rate of increase in the frequency of obesity continues (4-8). In COSI TUR 2016 research study conducted in 67 provinces representing Turkey, when body mass index (BMI) of 2nd grade elementary school children were assessed according to Z-Score, 9.9% were found to be obese and 14.6% were found to be overweight; however, in the previous COSI 2013 research, obesity was determined as 8.3% and the percentage of overweight children was determined to be 14.2%. The rate of obese and overweight children are observed to increase in the more recent study compared to COSI 2013 report (9). There is still no specific treatment strategy in developed countries despite the serious increase in the obesity rate in childhood in the last 30 years and most of the performed studies are directed towards prevention of childhood obesity (2-6).

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ETIOPATHOGENESIS

Epigenetics is a term that refers to the hereditary rearrangement of gene expression without alteration in the base sequence of DNA. Epigenetics is thought to play a major role in the serious increase in obesity during the past 30 years. Children with obese parents are at high risk for obesity. If one of the parents is obese, then the risk is 30%, however if both of the parents are obese, then the risk of obesity for the child is 90% (1-5,10-12). In addition, excessive weight gain during pregnancy, tobacco use, gestational diabetes mellitus increases the risk of obesity in children. Toxins, drugs, infections, and exogenous hormones are considered to be other conditions that result in obesogenic epigenetic changes. Exposure to environmental endocrine disrupting chemicals such as pesticide dichlorodiphenyl-trichloroethane or bisphenol A were found to increase the likelihood of triggering or aggravating obesity in some epidemiological studies. Though genetic factors play a role in a person's susceptibility to obesity, an obesogenic environment must be for present for phenotypic expression (3-7,10-12).

Various environmental factors contribute to the development of obesity. Sedentary lifestyle due to industrialization is the biggest threat in the formation of obesity. Sedentary lifestyle despite excessive and fast eating are the most important reasons for obesity in children. The presence of environmental factors such as increased intake of foods with high glycemic index, sugar-containing drinks, corn starch foods and beverages, large portions of ready-made foods, fast food service, reduced habit of eating with the family, decreased physical activity, shortened sleep time and scarcity of playgrounds contribute to the development of obesity. Duration of watching television is one of the most environmentally related effects on the development of obesity in childhood. Playing electronic games has also been associated with obesity in childhood with weaker effect on obesity compared to watching television. This has been attributed to the fact that electronic games do not contain food ads (2-7,13).

In recent years, intestinal microbiota has been an important focus in the investigation of the obesogenic environment. Many studies have shown that obesity and its complications are associated with changes in intestinal microbiota. Some researchers have suggested that there is a relationship between the bacteria settled in the intestinal tract with the potential for weight gain. Animal studies have shown that administration of antibiotics early in life increases the susceptibility to obesity. Although many observational studies and meta-analyses support this possibility, it has been suggested that the magnitude of this effect may be minor or even clinically insignificant. A relationship between prenatal antibiotic exposure and obesity in early childhood was reported. In another extensive study in which a relationship between antibiotic exposure in early infancy and subsequent weight gain could not be found, exact opposite results were observed. Whether these mechanisms are related to human obesity, or not, and if this is the case, whether they significantly contribute to obesity epidemic, or not remains uncertain (5-8,10-14).

DIAGNOSIS

Weight assessment in children with obesity is made according to the child's age and the severity of obesity. The goal of measurement methods is to determine the ratio of adipose tissue and lean tissue. Direct and indirect methods are used to measure body fat. Body mass index (BMI) is a commonly used indirect method recommend by WHO in field studies related to clinical obesity, rather than direct fat measurements such as X-ray absorptiometry, whole-body magnetic resonance imaging, and bioelectrical impedance analysis, which are expensive, laborious and difficult methods for measuring fat mass. Body mass index is the most practical and reliable method used in defining obesity (2-8,15-17). BMI is not used in children up to 2 years old. Instead, the weight percentile of the children is compared with the height percentile. Children who have a higher increase in weight percentage than height percentage should be closely monitored. BMI charts are used for children between the ages of 2-20. Specific percentile curves have been created for our country starting with infancy. BMI's of 85-94% (> 1.5SD) percentile indicates overweight, and BMI being over 95% (> 2SD) indicates obesity according to age and gender between the ages of 2-20. In normal children, there is a "J" shaped curve in both charts, since BMI decreases between the years 2-6 and increases between the years 6-20 (3-7). The initial decline and subsequent increase in BMI is called the "adiposity rebound". If a child does not have a decrease in BMI or has an early rise between the ages of 2-6, then that child is at risk for obesity. Today, quiet practical calculation methods have been developed with the utilization of technology (15-17). BMI SD and percentile calculations

according to the height and weight standards of children of our country can be easily calculated with a program developed by the Association of Child Endocrinology and Diabetes. It is possible to access the program called ÇEDD-Oksoloji / ÇEDD Çözüm via smart phones (https://www. https://www.ceddcozum.com/Home/Change?LanguageAbbreviation=tr). It is an easy-to-use practical program and can be used to define obesity in children and to evaluate their height percentiles.

DIFFERENTIAL DIAGNOSIS

Childhood obesity is generally exogenous (primary) type. There is no underlying pathology for this type. Exogenous obesity is basically caused by the fact that the calorie intake is more than the energy spent and therefore it is a preventable situation. Causes such as age, gender, genetics, nutritional habits, socioeconomic status and lack of physical activity plays role in the development of this condition. Secondary type obesity, having an incidence of less than 1% in childhood, develops due to another underlying pathology (genetic syndromes, endocrine or other causes) (4-8).

Taking a detailed history is very important to reveal the causes of secondary obesity in the approach to obesity disease. Family history, prenatal and postpartum history, postpartum medical care history should be taken in detail. Diet history should be questioned; breastfeeding time, bottle feeding, transition to supplementary foods should be noted. The activities of the child should be questioned; exercises or daily activities, sleep time and duration, as well as obesity-related comorbid diseases should be investigated, history of known diseases and drug use should be questioned. The psychological health of the child should also be questioned and it should be understood whether the onset of obesity is related to intense stress (traffic accident, loss of parents or friends, etc.), or not. Increased eating behavior may be associated with feelings of pleasure and stress relief (1,3,6-8).

Differential diagnosis in children with obesity begins with the evaluation of linear growth. Accelerated linear growth is observed in children with exogenous obesity. These children are at risk for the early development of their secondary sexual characteristics and their bone age may also be more than their chronological age. Children with obesity due to an underlying endocrinopathy have decreased linear growth. Acquired hypothyroidism, cortisol excess (corticosteroid therapy, Cushing Syndrome), growth hormone deficiency, and pseudohypoparathyroidism are examples of endocrine disorders causing childhood obesity. These disorders are usually associated with overweight or mild obesity rather than severe obesity. Endocrine causes were found in few of the obese children who were enrolled in many retrospective studies. Routine laboratory examinations directed to endocrine causes are not recommended if the patient's height is not shorter than his/her genetic potential and/or growth rate has not decreased according to age and gender (1,4,5,7,8).

Monogenic obesity should be considered in children who gained excess weight in early infancy, especially in children with severe obesity before the age of 5. These children may develop developmental delay, short height, dysmorphic face, and hyperphagia. Though Prader Willi, Bardet-Biedl, Fragile-X, Albright hereditary osteodystrophy, Alström syndrome, congenital leptin deficiency, proopiomelanocortin (POMC) deficiency, MC4R deficiency and Cohen's syndrome are obesity-related syndromes, other genetic causes that are not associated with these syndromes might also be present. Syndromic and genetic causes should come to mind at first in the presence of short stature, mental retardation, bone age retardation, and findings of pathological physical examination (1,4-7).

PHYSICAL EXAMINATION

Physical examination is both important and difficult in children with obesity. In particular, adolescent patients may wear loose clothing or tight corsets to hide their obesity thus the clinician should be careful about this. Moreover, increased adipose tissue or increased hair growth are other reasons that make physical examination difficult. It is not always easy to determine early thelarche in girls or gynecomastia in boys (4,7,8). Attention should be paid to skeletal system problems in children with obesity. Children with curvature in their legs should be evaluated in terms of Blount Disease (tibia vara) and additional radiological examinations should be requested. Although scoliosis is more common in obese children than in children with normal weight, its diagnosis is more difficult due to excessive fat. The clinician should keep the possible skeletal problems in mind and request further radiological examination when necessary. In addition, physical examination should be extended according to the patient's additional complaints such as neck circumference, and tonsils should be examined in a patient suffering from snoring (3-8),

Relationships between obesity and a wide range of health problems such as cardiovascular diseases, metabolic diseases, respiratory system diseases, chronic diseases (hypertension and diabetes), dyslipidemia, sleep apnea syndrome, asthma, polycystic ovarian syndrome, depression and quality of life deterioration, non-alcoholic liver steatosis, femoral head epiphysis shift have been found in previous studies (3-7).

OBESITY COMORBIDITIES

Hypertension

It is more common in obese children than in children with normal weight. Activation of the sympathetic system, increased sodium reabsorption, hyperinsulinemia, activation of renin angiotensin aldosterone are factors facilitating hypertension (HT) in obesity. Three separate measurements should be made at least 1 week apart for the diagnosis of HT. Values for the diagnosis of HT differ by age in children. It should be performed by evaluating normal levels according to age, gender and height in children under 13 years of age. Blood pressure is ordinarily lower at night. Blood pressure measured at night should normally show a reduction of up to 10%. Disruption of this circadian rhythm in childhood obesity is considered as an early sign of hypertension. In children diagnosed with stage 2 HT, final organ damage should be evaluated. In particular, kidney function tests should be requested. Primarily a lifestyle change and diet should be tried for treatment. Low sodium is recommended for diet. Although weight loss constitutes the basis of HT treatment in obese children, pharmacotherapy should be initiated in patients with persistent HT or in patients with end organ damage (3,6,18).

Dyslipidemia

This disease is more common in obese children, characterized by high triglyceride and low HDL levels. Dyslipidemia associated with obesity responds very quickly to weight loss. Further research should be applied and primary dyslipidemia should be investigated in cases of dyslipidemia that do not respond to weight loss or manifest itself with different values than high triglyceride and low HDL levels (4,7,19).

Sleeping Disorders

Obese children may experience sleep disturbances such as snoring, sleep apnea syndrome, daytime sleepiness, hyperactivity, depression, and nocturnal enuresis with new onset. It is recommended that the clinician should be careful about this issue and make necessary clinical evaluations by questioning the sleep pattern (7,8).

Glucose Metabolism Disorders

Continued excessive energy intake leads to impaired glucose metabolism and insulin resistance in obese individuals. Insulin resistance is associated with obesity-related comorbidities and cardiometabolic risk. Insulin sensitivity is usually evaluated by hyperinsulinemic euglycemic clamp tests or frequent blood sampling for plasma insulin and glucose concentrations with intravenous glucose infusion. However, these techniques are used rarely in daily practice. Evaluation of insulin sensitivity based on fasting or post-meal glucose and insulin concentrations is clinically performed. These are HOMA-IR (homeostasis model of insulin resistance), QUICK index, and Matsuda index. HOMA-IR shows a high correlation with fasting insulin values in children and it is seen as a more suitable method to show insulin resistance compared to fasting insulin measurement alone. HOMA-IR normal values vary in different societies and age ranges. In a study by Kurtoğlu et al. insulin resistance in obese children was evaluated, the limit levels for HOMA-IR were calculated as 2.67 for prepubertal boys, 2.22 for prepubertal girls and 5.22 for pubertal boys, 3.82 for pubertal girls in our country (20-24).

Serum glucose screening is also recommended in obese children. While impaired fasting glucose is expressed as FBG 100-126 mg / dl in repeated measurements, impaired glucose tolerance means that BG is 140-199mg / dl at OGTT at the 2nd hour. These disorders may be associated with type 2 DM. However, HbA1C > 5.9% was suggested to be associated with insulin secretion, insulin sensitivity and B cell dysfunction (1,4,8).

Treatment

Necessary measures to prevent obesity should be taken at a very early period. Breastfeeding alone in the first 6 months and co-administration of supplementary foods after 6 months with should be recommended to parents who are in charge of taking care of the child in all child follow-up outpatient clinics. Fruit juice, sweet drinks and carbohydrate loaded formulas should be avoided after switching to supplementary foods. The family should be

involved in the nutritional management, the diet should be rich in vegetables and fruits, and foods containing carbohydrates with high glycemic index should be limited. Physical activity is another aspect that is as important as nutrition. Physical activity should be suitable for the child's age and should complement the daily nutrition plan. Active lifestyle and limitation of television and video games during the day is very important for the prevention of obesity (3,4,7,8).

Pharmacological treatment is very limited in the treatment of obesity in children and adolescents. Orlistat is the only drug approved by the FDA for the treatment of obesity in adolescents (> 12 years). Orlistat, a lipase inhibitor, prevents the absorption of approximately one-third of the fat taken in a meal. The recommended orlistat dosage is 120 mg 3 times a day with meals. Its efficacy was found to be limited in placebo-controlled studies. Diarrhea, abdominal pain, bloating and fatty stool are among the side effects that limit the use of orlistat. It is recommended to take a multivitamin when using orlistat, since it prevents the absorption of fat-soluble vitamins. Phentermine is another FDA-approved drug for short-term treatment (12 weeks) over the age of 16 years. There are few studies on phentermine which is an asympathomimetic amine derivative. Blood pressure and heart rate should also be evaluated during screening and monitoring for heart disease before use. Topiramate and glucagon-like peptide-1 analogs are found among other drugs that have not been approved for the treatment of obesity in children. Studies on these pharmacotherapies were uncontrolled and the number of cases were insufficient, more experience seems to be necessary to understand the efficacy of these medications in obesity treatment (1,3,7,8).

One of the most frequently used drugs in clinical practice is metformin though it is not approved by the FDA in treatment of obesity. Metformin is approved for Type 2 DM. Its short-term use can be recommended with expert opinion and is frequently used by pediatric endocrine specialists if obesity is accompanied by acanthosis nigricans, glucose metabolism disorders and other comorbidities such as polycystic ovary syndrome (PCOS). Metformin is a guanidine derivative used in child and adult Type 2 DM. It reduces fasting hyperinsulinemia and prevents Type 2 DM, and supports weight loss in some obese individuals by increasing hepatic and muscle insulin sensitivity. It is contraindicated to use in cases such as kidney failure, congestive heart failure, lung failure and liver failure. Nutrition and lifestyle changes should be tried at first for type 2 DM treatment. Pharmacologically, metformin having FDA approval can be used in children over the age of 10. The first treatment option should include lifestyle changes where healthy nutrition and physical activity are enhanced whether insulin resistance is present in obesity, or not. Exercise increases hepatic glucose uptake and glycogen synthesis and reduces hepatic glucose production, thereby lowers fasting glucose and insulin levels (3,8,24,25).

Obtaining positive results after bariatric surgery procedures for severe obesity in adolescents similar to adults has increased the popularity of this method in recent years. Roux-en-Y gastric bypass and sleeve gastrectomy are the methods that are generally used in these age groups. Insufficient number of patients and follow-up duration, and lack of standardization of the procedures may be considered the limitations of the studies on this subject. This method, which is not a part of the routine treatment, can be applied in selected cases, with the decision of a multidisciplinary team experienced in adolescents with severe obesity and comorbid diseases, who cannot lose weight despite drug treatment (3,6,7,26).

CONCLUSION

Childhood obesity is a preventable condition that also reflects into adulthood and causes important problems. Obesity is an important disease causing type 2 diabetes mellitus, hypertension, cardiovascular diseases, osteoporosis and some types of cancer. In addition, obesity adversely affects a person's social life, reduces self-esteem and can cause mental problems. It is important to recognize these children as early as possible to investigate and prevent possible pathologies. The goal of managing a child with obesity should be not only to reduce BMI, but also to prevent complications and reduce existing comorbidities. It is difficult to treat when obesity and associated comorbid conditions develop, therefore primary prevention appears to be more effective in these situations. The lack of sufficient evidence-based research on the management of obesity in children prevents the application of analytical clinics. The development of the pediatric obesity algorithm will enable it to be used by experts as a comprehensive evidence-based road map for the diagnosis and management of children with obesity.

Declarations

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ORIGINAL ARTICLE

The Role of Irisin, Copper and Zinc Levels on Insulin Resistance in Polycystic Ovary Syndrome

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Abstract

Background: Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. Irisin is defined as a myocin released from skeletal muscle that protects individuals from metabolic diseases when exercised regularly. Zinc is thought to play an active role in the pathophysiology of PCOS in relation to insulin resistance. Copper has been stated to contribute to oxidative stress and insulin resistance in PCOS patients. The aim of this study was to evaluate the relationship between serum irisin, copper and zinc levels and insulin resistance in PCOS patients and control cases.

Methods: Our study consists of a patient group of 45 individuals diagnosed with PCOS and a healthy control group of 45 individuals. 2003 Rotterdam diagnostic criteria were used for the diagnosis of PCOS. Serum copper, zinc and irisin levels were measured and evaluated with regard to Body Mass Index and insulin resistance.

Results: Serum zinc and copper levels were found to be higher in PCOS patients compared to controls ($p<0.05$), however no statistically significant differences were found between the groups with regard to HOMA-IR and serum irisin levels.

Conclusions: It was evaluated that the data obtained from the patient group in this study may have been effected due to patients' use of some medications like metformin, multivitamin supplements and oral contraceptives.

Key words: PCOS, Irisin, Insulin Resistance, Copper, Zinc.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex endocrinopathy most prevalent in women of reproductive age with an incidence of approximately 5-10%. PCOS is a condition characterized by hyperandrogenism, oligomenorrhea, amenorrhea and polycystic ovaries. Clinical reflection is often in the form of menstrual dysfunction, cosmetic problems, or infertility. PCOS is considered as an important public health issue due to the risks it poses for a long period of time (1-3). PCOS can be defined as a frequent syndrome that is encountered as a result of interaction of complex, environmental and

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genetic factors, although its etiology is not fully known. In the pathophysiology of PCOS, the effects of insulin and its secretion disorders, gonadotropin changes, as well as genetic factors are at the forefront (4-6). Insulin resistance (IR) is believed to play an important role in the pathophysiology of PCOS. Despite numerous clinical and experimental studies, its etiology is still unclear (7, 8). Moreover, IR plays a critical role in the development of metabolic syndrome and cardiovascular diseases in women with PCOS. IR increases susceptibility to long-term dyslipidemia, type 2 diabetes, hypertension, cardiovascular heart diseases (8).

Obesity has attracted attention in recent years as a global public health problem (9, 10). Overweight and obese individuals constitute approximately 65% of the world population. Inadequate energy homeostasis is the main cause of obesity. High energy intake and/or low energy consumption cause inadequate energy homeostasis (11). Obesity negatively affects IR and triggers the risk of diabetes mellitus (DM) and cardiovascular diseases. Considering these, treating obesity should be the primary target for women with PCOS. Thus, long-term health problems may be prevented (12).

Irisin, a protein hormone consisting of 112 amino acids is secreted from adipose tissue (13). Irisin, a thermogenic protein, turns white adipose tissue into brown adipose tissue, thereby causing energy expenditure and is thought to play an important role in reducing fat mass (11, 14). Studies have shown that serum irisin level is associated with metabolic diseases including type 2 diabetes, obesity and metabolic syndrome (15). Some cytokine secretions are irregular in PCOS which may be playing a role in IR pathophysiology. The role of irisin in PCOS development is still uncertain. Although human and animal studies suggest a correlation between irisin and obesity and IR-related metabolic parameters, the results are inconsistent. In particular, the relationship between the circulating irisin and the different features or phenotypes used for the diagnosis of PCOS remains uncertain. It has been stated that more studies are needed to understand the direct relationship between irisin and IR in women with PCOS (16-21).

Zinc is an essential trace element and is necessary for many cellular functions. The role of metalloproteins in the function of inducing members of the hydrolase, ligase, oxidoreductase and lyase family is important. It functions as a cofactor for many enzymes (more than 300) and as a transcription factor in the body. Zinc is involved in many metabolic processes, including carbohydrate, lipid, protein and nucleic acid synthesis and degradation. Zinc deficiency causes many chronic diseases (22-25). Zinc, which is an antioxidant, prevents the formation of free radicals and has a protective role against oxidative stress. Moreover, zinc plays a role in the pathogenesis of rheumatological inflammatory diseases, alcoholism, liver cirrhosis and cardiovascular diseases caused by oxidative damage (26, 27). Scientific research shows that plasma zinc levels are low in obese individuals. Zinc deficiency can cause glucose intolerance and insulin resistance (28). Many studies have investigated serum zinc levels in patients with PCOS, but the results of these studies have been insufficient (29). Some studies have demonstrated that serum zinc levels in women with PCOS are higher than healthy women (30). Other studies have reported that circulating zinc levels in women with PCOS are lower (30-32).

Copper acts as a biocatalyst in human metabolism and is found in the structure of many metalloenzymes and some natural pigments (32, 33). It has been stated in some studies that the increase of oxidative stress may be effective in the pathogenesis of PCOS (34). Copper has been found to induce oxidative stress as a catalyst in the formation of reactive oxygen species while reducing glutathione levels. Copper, which normally binds to proteins, can also be released to perform Fenton-type reactions where hydroxyl radicals are produced. Oxidative stress can also increase due to hyperglycemia, insulin resistance and higher levels of free fatty acids. The induction of oxidative stress causes an increase in the production of reactive oxygen species (35-37).

The aim of this study was to evaluate the relationship between serum irisin, copper and zinc levels and insulin resistance in normal weight, overweight and obese PCOS patients and the control group.

MATERIALS AND METHODS

This study was approved by the Selcuk University Medical Faculty Ethics Committee (Date: 08.05.2019, No: 2019/114) where the study was conducted. The study was explained to the patients and informed written consents were obtained from all participants.

In our study, 16 obese, 10 overweight and 19 normal weight PCOS patients were included in the patient group (n=45) and 12 obese, 14 overweight and 19 normal weight healthy individuals were included in the control group (n=45). A total of 90 individuals were included in our study. For the diagnosis of PCOS, 2003 Rotterdam diagnostic criteria were used. The patients were between 15-44 years old and Body Mass Index (BMI) values were 18.5-40 kg/m2. Overweight is defined as a BMI of 25-29.9 kg/m², while a BMI ≥ 30 kg/m² defines obesity. If BMI was below 25 kg/m², it was considered normal weight. Patients included in the study did not have accompanying chronic diseases. Patients with previously diagnosed Cushing's disease, hypertension and cardiovascular diseases were not included in the study. Serum copper and zinc levels were measured by an Atomic Absorption Spectrometer (Varian AA240FS), serum irisin levels were measured by a commercial ELISA kit (Elabscience, Catalog No: E-EL-H6120). Glucose and insulin measurements were done with routinely used methods. Insulin resistance was estimated by homeostasis model assessment of insulin resistance (HOMA-IR). HOMA-IR was calculated according to the following formula: [Fasting insulin (μU / ml) X fasting glucose (mg/dl)] / 405. BMI values (kg/m2) were calculated as the ratio of the body weight (kg) to the height squared (m2).

STATISTICAL ANALYSIS

Data were analyzed by using statistical SPSS 25 software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). The homogeneity of variances was checked with the "Levene test". The distribution of the variables was analyzed with the "Shapiro–Wilk test". "Independent Student's t-test" was used for comparing differences of normally distributed variables between two groups. Mann Whitney U test was used for non-parametric distributed values. Data were presented as mean ± standard deviation (SD) for normally distributed variables. Correlation analysis was carried out with Pearson's and Spearman's correlation tests. "p" values lower than <0.05 was considered to be statistically significant.

RESULTS

In our study, a statistically significant difference was found with regard to serum zinc and serum copper levels in PCOS patients compared to the control group ($p < 0.05$). Serum zinc and serum copper levels were found to be higher in patients with PCOS compared to individuals in the control group **(Table 1).**

Table 1. Comparison of Parameters in Patient and Control Groups.

Parameter	Patient Group (n=45) (Mean±SD)	Control Group (n=45) (Mean±SD)	p
Irisin (pg/ml)	191.48±180.97	237.32±221.54	0.327
Zinc (μmol/L)	15.90±3.45	13.34±3.58	**0.001**
Copper (μg/dL)	147.72±40.28	118.13±41.65	**0.001**
Glucose (mg/dl)	81.98±13.39	83.58±14.08	0.805
Insulin (μU/mL)	9.75±4.28	8.99±3.65	0.369
HOMA-IR	2.02±1.0	1.9±0.95	0.580

Homa-IR: homeostasis model assessment of insulin resistance

According to the results obtained in the study, negative correlation between copper and irisin (r: -0,215, $p<0.05$) and positive correlation between zinc and copper (r: 0,483, $p<0.01$) were found. There was a negative correlation between insulin and irisin (r: -0,235, $p<0.05$); positive correlation between glucose and insulin (r: 0,320, $p<0.01$), negative correlation between HOMA-IR and irisin (r: -0,241, $p<0.05$); positive correlation between glucose and HOMA-IR (r: 0,593, $p<0.01$) were observed. A positive correlation between insulin and HOMA-IR (r: 0,938, $p<0.01$) was also identified **(Table 2).**

Table 2. Correlation analysis results between all variables for all patients

n=90		Irisin (pg/ml)	Zinc (µmol/L)	Copper (µg/dL)	Glucose (mg/dl)	Insulin (µU/mL)
Zinc (µmol/L)	r	-0.123				
	p	0.246				
Copper (µg/dL)	r	**-.215***	**.483****			
	p	0.042	0.001			
Glucose (mg/dL)	r	-0.122	-0.003	0.115		
	p	0.251	0.975	0.279		
Insulin (µU/mL)	r	**-.235***	-0.007	0.161	**.320****	
	p	0.026	0.946	0.130	0.002	
HOMA-IR	r	**-.241***	-0.007	0.157	**.593****	**.938****
	p	0.022	0.946	0.140	0.001	0.001

***p<0.05. ****p<0.01.**

When obese individuals in the PCOS and control groups were compared, a statistically significant difference between serum zinc and serum copper levels were found (p<0.05). Serum zinc and serum copper values were higher in obese individuals with PCOS than those in the control group **(Table 3).**

Table 3. Comparison of parameters in obese patients and controls.

Parameter	Obese Patient Group (n=16) Mean±SD	Obese Control Group (n=12) Mean±SD	p
Irisin (pg/ml)	194.75244.5	107.869.31	0.486
Zinc (µmol/L)	16.694.17	10.953.39	**0.001**
Copper (µg/dL)	141.5333.53	93.5832.47	**0.001**
Glucose (mg/dl)	85.1312.92	94.017.33	0.226
Insulin (µU/mL)	13.333.73	11.953.75	0.345
HOMA-IR	2.841.00	2.791.03	0.898

According to the results obtained in obese PCOS patients and control individuals, positive correlation between copper and zinc (r: 0,644, p<0.01), positive correlation between insulin and copper (r: 0,432, p<0.05), positive correlation between HOMA-IR and copper (r: 0,391, p<0.05), positive correlation between glucose and HOMA-IR (r: 0,591, p<0.01), and positive correlation between insulin and HOMA-IR (r: 0,881, p<0.01) were observed **(Table 4).**

Table 4. Correlation analysis results between all variables for obese individuals

n=28		Irisin (pg/ml)	Zinc (µmol /L)	Copper (µg/dL)	Glucose (mg/dl)	Insulin (µU/ mL)
Zinc (µmol/L)	r	-.086				
	p	.662				
Copper (µg/dL)	r	.118	**.644****			
	p	.551	.001			
Glucose (mg/dl)	r	-.124	.054	.148		
	p	.528	.786	.451		
Insulin (µU/ mL)	r	.139	-.023	**.432***	.164	
	p	.482	.909	.022	.403	
HO-MA-IR	r	.067	.008	**.391***	**.591****	**.881****
	p	.734	.967	.040	.001	.001

***p<0.05. ****p<0.01.**

When overweight individuals in the PCOS and control groups were compared with regard to all parameters, there was no statistically significant difference between the two groups.

According to the results we obtained in overweight PCOS patients and control individuals, a positive correlation between insulin and copper (r: 0,434, p<0.05), HOMA-IR and glucose (r: 0,606, p<0.01), and insulin and HOMA-IR (r: 0,949, p<0.01) were observed **(Table 5).**

Table 5. Correlation analysis results between all variables for overweight individuals

n=24		Irisin (pg/ml)	Zinc (µmol/L)	Copper (µg/dL)	Glucose (mg/dl)	Insulin (µU/mL)
Zinc (µmol/L)	r	.146				
	p	.495				
Copper (µg/dL)	r	-.024	-.075			
	p	.911	.728			
Glucose (mg/dl)	r	.221	-.106	.086		
	p	.300	.622	.691		
Insulin (µU/mL)	r	-.206	-.093	**.434***	.357	
	p	.333	.665	.034	.087	
HOMA-IR	r	-.124	-.091	.355	**.606****	**.949****
	p	.563	.671	.089	.002	.001

***p<0.05. ****p<0.01.**

When normal-weight PCOS patients and control individuals were compared, a statistically significant difference in serum copper levels were determined (p <0.05). Serum copper values were found to be higher in PCOS patients compared to controls **(Table 6).**

Table 6. Comparison of parameters in <u>normal-weight</u> patients and controls.

Parameter	Normal Weight Patient Group (n=19) Mean±SD	Normal Weight Control Group (n=19) Mean±SD	p
Irisin (pg/ml)	178.01140.28	289.79245.9	0.204
Zinc (µmol/L)	15.283.03	13.493.18	0.084
Copper (µg/dL)	163.3445.80	117.6348.57	**0.005**
Glucose (mg/dl)	81.1113.28	80.4710.45	0.871
Insulin (µU/mL)	7.693.15	7.543.18	0.99
HOMA-IR	1.570.63	1.520.73	0.805

According to the results obtained in patients with normal-weight PCOS and control individuals, negative correlation between zinc and irisin (r: -0,389, p<0.05), negative correlation between copper and irisin (r: -0,546, p<0.01); positive correlation between zinc and copper (r: 0,592, p<0.01), negative correlation between insulin and irisin (r: -0,379, p<0.01), negative correlation between HOMA-IR and irisin (r: -0,433, p<0.01), positive correlation between copper and HOMA-IR (r: 0,335, p<0.05), positive correlation between glucose and HOMA-IR (r: 0,435, p<0.01) and positive correlation between insulin and HOMA-IR (r: 0,926, p<0.01) were observed **(Table 7).**

Table 7. Correlation analysis results between all variables for normal-weight individuals

n=38		İrisin (pg/ mL)	Zinc (µmol/L)	Copper (µg/dL)	Glucose (mg/dl)	İnsulin (µU/mL)
Zinc (µmol/L)	r	**-.389***				
	p	.016				
Copper (µg/dL)	r	**-.546****	**.592****			
	p	.001	.001			
Glucose (mg/dl)	r	-.205	.074	.254		
	p	.217	.659	.124		
İnsulin (µU/mL)	r	**-.379***	.177	.263	.122	
	p	.019	.287	.111	.464	
HOMA-IR	r	**-.433****	.171	**.335***	**.435****	**.926****
	p	.007	.305	.040	.006	.001

***p<0.05. ****p<0.01.**

DISCUSSION

PCOS, although its etiology is not fully known, can be defined as a frequently encountered syndrome that occurs as a result of the interaction of complex, environmental and genetic factors. In the pathophysiology of PCOS, the effects of insulin and its secretion disorders, gonadotropin changes, as well as genetic elements are considered very important (5, 6)

Irisin is a cleavage protein of fibronectin type III domain 5 (FND5). It significantly reduces activity in skeletal muscles in women with PCOS. In a meta-analysis by Wang et al., irisin levels were found to be higher in PCOS patients than in control individuals, but they did not report a significant correlation between circulating irisin levels and IR in their population (18). In the studies by Gao et al. and Pukajło et al., no significant difference with regard to serum irisin levels were found between PCOS patients and control individuals (19, 20). In our study, serum irisin levels of patients with PCOS were lower than the control group (the difference was not statistically significant). There was also a negative correlation between insulin and HOMA-IR, and irisin levels. Serum irisin levels of obese PCOS patients were higher than the obese control group (the difference was not statistically significant). Serum irisin levels in normal-weight PCOS patients were lower than control group participants (the difference was not statistically significant). A negative correlation was observed between HOMA-IR and irisin. In women with PCOS, the function of the receptor-gamma coactivator 1 alpha (PGC 1-a), which is activated by degraded peroxisome proliferator is considerably repressed. This leads to changes in the expression and function of irisin. The (statistically non-significant) low irisin levels in PCOS patients observed in this study are thought to be caused by the repression of PGC-1a.

Copper (Cu) acts as a biocatalyst in human metabolism and is found in the structure of many metalloenzymes and some natural pigments (32). It has been reported in some studies that an increase in oxidative stress levels may play a role in the pathogenesis of PCOS (38). In the studies by Kurdoğlu et al., Kanafchian et al. and Celik et al. serum Cu levels of PCOS patients were found to be significantly higher than the control group (36). High Cu levels have been shown to be associated with an increased risk of early cardiovascular diseases (36, 37, 39). In the present study, serum Cu levels were higher in PCOS patients than in the control group. Cu levels were found to be higher in PCOS patients regardless of BMI. A positive and statistically significant correlation was found between HOMA-IR and Cu. Increased IR may cause increased oxidative stress, which may lead to increased Cu levels in individuals with PCOS. Further studies that include reactive oxygen species as a parameter may be useful in order to clarify the relationship between high Cu levels in PCOS patients.

Zinc (Zn) is an essential trace element that is fundamental for many cellular functions. Zn is involved in many metabolic processes, including carbohydrate, lipid, protein and nucleic acid synthesis and degradation. Zn deficiency causes many chronic diseases (22, 36, 39). In a study conducted by Kurdoğlu et al, zinc levels of PCOS patients were found higher than the control individuals. However, these values remained within the reference range (10,7-17,5 μmol/L) (39). In the study conducted by Chakraborty et al, although zinc levels of PCOS patients were higher than the control individuals, no statistically difference was found (32). In a study by Kulhan et al. values also remained within the reference range (10,7-17,5 μmol/L). In another study by Kanafchian et al. significantly lower results were found in patients with PCOS compared to the control group (30, 31). In the present study, serum zinc levels were higher in PCOS patients compared to the control group. In addition, zinc levels in obese PCOS patients were higher than the obese individuals in the control group and there was a statistically significant difference which remained in the reference range (10.7-17.5 μmol/L). No relationship was found between HOMA-IR and zinc levels. The higher zinc levels may be specific to women in Turkey as an ethnic difference. Serum zinc levels being in the reference range may be the reason for HOMA-IR and zinc levels not to be correlated.

In conclusion, serum Zn and Cu levels were found to be higher in PCOS patients compared to controls, however no statistically significant differences were found between the groups with regard to HOMA-IR and serum irisin levels. Data obtained from the patient group in this study may have been effected due to their use of some medications like metformin, multivitamin supplements and oral contraceptives.

Further studies with higher number of participants may improve the distinction of the variables like irisin and HOMA-IR between the PCOS patients and controls.

Declarations

This research was supported by Scientific Research Projects of Selcuk University with project number 19202059.

There is no conflict of interest.

This study was approved by the Selcuk University Medical Faculty Ethics Committee (Date: 08.05.2019, No: 2019/114) where the study was conducted. The study was explained to the patients and informed written consents were obtained from all participants.

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ORIGINAL ARTICLE

Retrospective Cross-Sectional Analysis of Treatment Processes of Children Diagnosed with Obsessive Compulsive Disorder

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Abstract

Background: Obsessive-compulsive disorder (OCD) is a severe, common and most often chronically debilitating disorder characterized by repetitive, ritualistic, and distressing thoughts, ideas, and behaviors. In this retrospective study, we have presented patients who have admitted to our clinic and was diagnosed with obsessive-compulsive disorder and their baseline and after-treatment symptom severity.

Methods: Participants who admitted to Aksaray University Faculty of Medicine Department of Child Adolescent Psychiatry were evaluated. Medical records were obtained by previous clinical evaluation and scaled scores for this retrospective study. The Schedule for Affective Disorders and Schizophrenia for School Age Children- Present and Lifetime Version, DSM-5 (K-SADS-PL) was applied to every patient at first session of treatment. Symptom severity of OCD was recorded according to Children's Yale-Brown Obsessive-Compulsive Scale.

Results: 73 patients were included in the study. 49.3% was male, 50.7% was female. 52.1% of patients have one or more comorbid disorders. All patients were using at least one pharmacological agent. There was a significant difference between baseline and eight weeks after treatment CY-BOCS total scores ($p<0.001$).

Conclusions: As a conclusion, pediatric OCD is a common and serious psychiatric disorder and SSRI medication is an effective choice. Compliance to treatment and regular follow-up is important for improvement.

Key words: Pediatric, Obsessive-Compulsive Disorder, Adolescent, Treatment.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a severe, common and most often chronically debilitating disorder characterized by repetitive, ritualistic, and distressing thoughts, ideas, and behaviors (1). Research suggests approximately 50% of all cases have their onset in childhood or adolescence (2). Obsessions and compulsions in children are more likely to change/evolve as well as wax and wane, compared to the course of the disorder in adults. An epidemiological study conducted in USA reported that 21% of OCD cases had onset by age 10 (3). Pediatric OCD appears to be more common in males than in females, in contrast to adults where the male-female ratio of OCD is approximately 1:1 (4).

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Treatment of OCD in children and adolescents include cognitive behavioral therapy (CBT) and selective serotonergic reuptake inhibitors (SSRIs) (5). For mild to moderate cases of pediatric OCD, CBT is suggested as first-line treatment. An SSRI can also be used as first-line treatment in cases of patient and family preference or if CBT is not suitable. For more severe cases, a combination of an SSRI and CBT is suggested as first-line treatment. The SSRI may be needed to decrease the OCD and associated anxiety symptoms to a level where CBT can be effective (6). Medications with demonstrated efficacy as monotherapy in children and adolescents with OCD include three selective serotonin reuptake inhibitors (SSRIs; fluoxetine, fluvoxamine, and sertraline) and a serotonergic, tricyclic antidepressant, clomipramine. One of the SSRIs as first-line choice of medications is suggested.

In this retrospective study, we have presented patients who admitted to our clinic and were diagnosed with obsessive-compulsive disorder and the patients' baseline and after-treatment symptom severity.

MATERIALS AND METHODS

Study protocol was approved by the Non-Interventional Ethics Committee of Aksaray University (Date: 30.04.2020, No: 2020/05-01).

Participants who admitted to Aksaray University Faculty of Medicine Department of Child Adolescent Psychiatry were evaluated retrospectively. Study protocol was approved by the Non-Interventional Ethics Committee of Aksaray University. Medical records were obtained by previous clinical evaluation and scaled scores for this retrospective study.

Patients who admitted to the outpatient child and adolescent psychiatry clinic, were diagnosed as obsessive compulsive disorder (OCD) and followed in the same clinic were included. Sociodemographic data were obtained from hospital records. The socioeconomic status was classified into three groups as low, moderate and high and scored according to parental education level, parental employment status, monthly household income level, the presence of a washing machine, dishwasher, computer and other technological devices in their home, and whether or not the child benefitted from education. Psychosocial stressors were accepted as difficult life conditions such as separated parents, mother or father working far from home, exposure to peer bullying, exposure to physical violence and loss of a loved one.

The Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version, DSM-5 (K-SADS-PL) was applied to every patient at first session of treatment. The Kiddie-schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL-DSM5), which is a semi-structured interview, was developed by Kauffman et al. (13) The initial reliability and validity of the data obtained with this scale in Turkey was carried out by Ünal et al. (14)

When the first Covid-19 case was recorded in Turkey, precautions against the pandemic were rapidly implemented. One of these precautions was restriction of non-emergency patients presenting at hospitals. Therefore, as recommended, the patients being followed up in outpatient clinics were contacted by telephone, and patient evaluations and follow-up after the outbreak of the pandemic were carried out as described (9). Within the context of the Covid-19 pandemic precautions, procurement of medications was facilitated for patients so that they could obtain their regular drug treatments from pharmacies without seeing a doctor.

Symptom severity of OCD was recorded according to Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS). In the follow-up, when a diagnosis of OCD was considered, CY-BOCS was applied to patients and follow-up was done accordingly. CY-BOCS, developed by Goodman et al. in 1986, is a semi-structured questionnaire based on clinical interviews (15). The patients were evaluated according to the clinical judgement of the interviewer based on the information given by the child and the parents. A total severity score was obtained from the obsession and compulsion severity points. An inter-observer reliability study of the scale in a Turkish sample was published by Yücelen et al (16).

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 23.0 for Windows software (SPSS Inc., Chicago, IL, USA). A value of $p<0.05$ was accepted as statistically significant.

RESULTS

773 patients were included the study. 49.3% was male, 50.7% was female. The mean age of the population was 12.82 (MIN=7, MAX=17). 19.2% of the patients had low, 58.9% had moderate and 21.9% had high socioeconomic status. The ratio of having a psychosocial stress factor before starting treatment was 26%. The mean duration between the beginning of obsessive-compulsive

symptoms and the time of diagnosis was 11.27 months (MIN=4 months, MAX=36 months). The mean follow-up duration after diagnosis was 6.39 months (MIN=3 months, MAX=16months)

52.1% of patients have one or more comorbid disorders. The comorbidity distribution data were as follows: 11% generalized anxiety disorder, 9.6% attention deficit hyperactivity disorder, 6.8% tic disorder, 6.8% social anxiety disorder, 2.7% panic disorder, %2.7 major depressive disorder, 2.7% specific learning disorder, 2.7% separation anxiety disorder, 2.7% trichotillomania, 2.7% oppositional defiant disorder, 1.4% nocturnal enuresis.

All the patients were given at least one pharmacological agent. In the monotherapy group, 66% of patients used fluoxetine 10-60 mg/day, 28% used sertraline 50-150 mg/day and 6% used clomipramine 25-75 mg/day. The combined pharmacological treatment ratio was 31.5%. In the combined treatment group, 21.9% of patients used antipsychotics (15.1% risperidone, 6.8% aripiprazole), 5.5% methylphenidate, 4.1% atomoxetine. 61.7% fluoxetine, 30.1% sertraline, and 8.2% clomipramine.

There was a significant difference between baseline (Mean=27.10) and eight weeks after treatment (Mean=14.16) CY-BOCS total scores ($p<0.001$). When severity scores were compared, there was a significant difference between baseline (Mean=3.7) and 8-week (Mean=1.9) severity scores ($p<0.001$). There was a significant difference between baseline CY-BOCS obsession scores ($p=0.026$) and CY-BOCS compulsion scores ($p=0.035$) between the monotherapy group and the combined therapy group. At the end of the 8-week treatment period, there was no significant difference between groups' CY-BOCS total scores ($p=0.809$).

DISCUSSION

In this study, we have presented retrospective data about patients diagnosed as OCD in our clinic. We have mentioned patients' sociodemographic characteristics, distribution of medical therapy choice and baseline and 8-week symptom severity.

Selective serotonin reuptake inhibitors (SSRIs) are the first-line medication of choice because of their efficacy and generally well tolerated side effect profile. SSRIs shown to be effective and safe in this population include fluoxetine, fluvoxamine, and sertraline (6). In a meta-analysis serotonergic antidepressants (SSRIs and clomipramine) are reported to reduce OCD symptoms compared to placebo. An overall effect size for medication versus placebo was 0.46 (standardized mean difference; 95% CI 0.37-0.55), equivalent to approximately four points on CY-BOCS (7). Similarly, we have found significant improvement in our patients. It was reported in the literature that more than half of the pediatric patients with OCD have been found to have at least one comorbid psychiatric disorder (8). Similar to this ratio, 52.1% of the patients in the present study have one or more comorbid disorders.

Specific SSRIs tested in clinical trials of pediatric OCD, all with positive results, include sertraline(5), fluoxetine(9) and fluvoxamine(10). In a clinical trial, 187 children and adolescents aged 13 to 17 years were randomly assigned to use sertraline (up to 200 mg/day) or placebo (11). Patients treated with sertraline showed greater improvement compared placebo-treated patients in rate of response (42% vs 26%) and reduction of OCD symptoms. Similar to these results, the most common medical agents used in the present study were fluoxetine and sertraline, respectively. Significant improvement was achieved with these agents.

Our study has certain limitations. The data was collected in one center and this is clearly a limitation when the results are supposed to represent a whole population. The follow-up period was limited to 8-weeks, thus, no long-term follow-up was carried out. Also, Comparison the effects of monotherapy and combined therapy were not compared because of the design of study.

As a conclusion, pediatric OCD is a common and serious psychiatric disorder and SSRI medication is an effective choice. Compliance to treatment and regular follow-up is important for improvement.

Declarations

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ORIGINAL ARTICLE

Do the Frequency of Ankle Joint-Related Pathologies Concomitant to Chronic Ankle Instability Vary According to Age and Gender?

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Abstract

Background: To determine the distribution of intra-articular lesions according to age and gender by retrospectively examining the archive records of patients who were operated due to ankle instability.

Methods: The patient records of ankle arthroscopy procedures from between February 2009 to February 2020 were retrospectively evaluated. The information about patients such as age, gender, surgical site, intra-articular and surrounding lesions (osteochondral defects, degenerative cartilage changes, synovial disorders, impingement syndromes, flexor hallucis longus lesions and the presence of os trigonum) were noted and compared statistically.

Results: The incidence of concomitant intra-articular pathology was found to be 78.2% in patients who underwent ankle arthroscopy due to instability. Anterior impingement syndrome in 74.5% of patients, osteochondral lesion in 41.2%, synovial hypertrophy in 15.8%, and degenerative arthritis in 9.1% of the patients were detected. The mean age of the patients with anterior impingement syndrome (p: 0.012), osteochondral defect (p: 0.001), and degenerative arthritis (p: 0.003) was found to be significantly higher than those without. The mean age of patients without additional pathology was 33.91±12.08, patients with an additional pathology were 37.77±12.35, and patients with more than one pathologies were found to be 42.15±11.79 (p: 0.003).

Conclusions: The most important finding of this study was that the presence and number of pathologies accompanying ankle instability increased with age. Considering the incidence of concomitant lesions in patients to be operated due to chronic ankle instability, detailed evaluation of preoperative magnetic resonance imaging and performing diagnostic arthroscopy may be beneficial for determining the possibility of concomitant lesions.

Key words: Ankle Instability, Age Distribution, Osteochondral Defects, Anterior Impingement Syndrome.

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INTRODUCTION

Intra-articular pathological lesions concomitant to chronic ankle instability are increasingly recognized and treated. Clinical studies report that more than 50% of patients with chronic ankle instability are accompanied by an intra-articular pathology (1). Moreover, it has been reported that 13-35% of patients has residual pain after successful ligament reconstruction. Ongoing pain is thought to be caused by accompanying intra-articular lesions (2). Intra-articular pathologies which frequently accompany chronic lateral ankle instability have been reported as tenosynovitis, anterolateral impingement lesion, attenuated peroneal retinaculum, ankle synovitis, intra-articular loose body, and osteochondral lesions (3, 4).

It has been reported in previous studies that increased age and female gender could be an indicator of poor prognosis after an ankle sprain. However, information on this subject is still believed to be insufficient; thus, it is recommended that clinical decisions for this group of patients should be made cautiously (5). In another study on chronic ankle instability, the mid-term clinical results of the surgery were discussed and it was shown that the presence of cartilage related lesions in older patients was associated with poor clinical outcome(6). Although magnetic resonance imaging is successful in detecting intra-articular lesions, the gold standard diagnostic method is still advocated to be diagnostic arthroscopy by many authors (7).

The aim of the present study was to determine the distribution of intra-articular lesions according to age and gender by examining the archive records of patients who were operated due to ankle instability retrospectively.

MATERIALS AND METHODS

The study was conducted in accordance with the principles of the Declaration of Helsinki and the protocol was approved by the ethics committee from the Gazi University (Date:14.07.2020; Decision Number: 07)

Hospital data files and video recordings of ankle arthroscopy - endoscopy procedures of patients between February 2009 and February 2020 were evaluated retrospectively. Patients who were operated due to ankle instability were included in the study and individuals under the age of 18, patients with insufficient archive records, ankle deformity, or a history of fractures were excluded from the study. Among the 682 ankle arthroscopy patients evaluated, 221 were found to meet the inclusion criteria. Fifty-six patients who met the exclusion criteria were excluded from the study. Age, gender, surgical side, intra-articular and surrounding lesions (osteochondral defects, degenerative cartilage changes, synovial disorders, impingement syndromes, flexor hallucis longus lesions and the presence of os trigonum) were noted for all 165 patients. The study was conducted in accordance with the principles of the Declaration of Helsinki and the protocol was approved by the ethics committee from the institute of the current study (Date:14.07.2020; Decision Number: 07)

All arthroscopic interventions were performed by the same surgical team and each procedure was started with a step-by-step arthroscopic examination of the ankle. After inserting the camera through the anteromedial portal to the ankle, the lateral gutter (ATFL's superior fascicle, resident's fibular tip), lateral talar dome, medial talar dome, medial gutter (deep layer of deltoid ligament, anterior tibiotalar ligament, the tip of the medial malleolus) and the medial tibial angle (notch of Henry) and anterior tibial rim were examined respectively. Detection of intra-articular pathologies was achieved by retrospective examination of arthroscopic examination in video recordings. Posterolateral and posteromedial portals were used in posterior ankle endoscopy, and endoscopic examination was performed after debridement.

Statistical analysis was performed using IBM SPSS Statistics, Version 23.0 (IBM Corp., Armonk, NY, USA), and a value of $p<0.05$ was considered statistically significant. Categorical variables were presented as numbers and percentages in statistical analysis, and continuous variables were presented as mean ± standard deviation (SD) in descriptive analysis. Chi-square tests were used to compare categorical variables in independent groups. The suitability of continuous variables to normal distribution was evaluated using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk tests). For independent variables, a t-test was used for comparing data sets with normal distribution, and the Mann-Whitney U test was used for variables that did not show normal distribution. In the case of 3 or more groups, analysis of continuous variables was performed using ANOVA for normal assumptions and the Kruskal-Wallis test for nonparametric assumptions.

RESULTS

The mean age of 67 male and 98 female patients included in the study was calculated as 38.8 ± 14.4 years (range: 18 - 67 years). The incidence of concomitant intra-articular pathology was found to be 78.2% in patients who underwent ankle arthroscopy due to instability. While 35.2% of the patients had pathology in addition to instability, 43% had more than one joint-related pathology. Anterior impingement syndrome in 74.5% of patients, posterior impingement syndrome in 9.7%, osteochondral lesion in 41.2%, synovial hypertrophy in 15.8%, degenerative arthritis in 9.1%, os trigonum in 3.6%, and flexor hallucis longus tendinitis in 2.4% was detected.

The mean age of the patients with anterior impingement syndrome (p: 0.012), osteochondral defect (p: 0.001) and degenerative arthritis (p: 0.003) as an additional pathology was found to be statistically significantly higher than those without (Table 1). When osteochondral defect patients were examined, it was observed that the mean age of 55 patients with medial lesions was 45.16 ± 10.72 and 31.81 ± 15.69 in patients with lateral lesions. There was also one patient with both medial and lateral lesions. This difference was statistically significant (p <0.001). The mean age of 15 patients with degenerative arthritis was 47.73 ± 13.84, while that of the others was 37.92 ± 11.94 (p:0.003).

Table 1: Differences in mean age according to the presence of ankle joint-related lesions

	Absent	Present	p value
Anterior Impingement Syndrome	34.69±12.57	40.22±12.08	0.012*
Posterior Impingement Syndrome	38.54±12.41	41.37±12.48	0.388
Talus Osteochondritis Dissecans	36.09±11.67	42.70±12.47	0.001*
Presence of Os Trigonum	38.64±12.34	43.50±14.52	0.348
Ankle Degenerative Arthritis	37.92±11.94	47.73±13.84	0.003*
Synovial Hypertrophy	38.48±11.94	40.61±11.80	0.423
*Independent samples t test			

Thirty-six (21.8%) patients had no additional pathology other than instability, fifty-five (33.3%) had one additional pathology, 69 (41.8%) patients had two additional pathologies, and the other 5 (3%) patients had more than two pathologies. When the distribution of patients by age was examined, the mean age of patients without additional pathology was 33.91 ± 12.08, patients with an additional pathology were 37.77 ± 12.35, and patients with two or more additional pathologies were found to be 42.15 ± 11.79 (Table 2, p: 0.003). No statistically significant correlation was found between gender and surgical side and variables (p>0.05).

Table 2: Distribution of intra-articular pathologies accompanying symptomatic acromioclavicular joint degeneration for all patients based on age groups

	Absent	Present	p value
Concomitant pathology	33.97±12.07	40.17±12.20	0.008*
Only one concomitant pathology	33.91±12.08	37.77±12.35	0.140
>1 concomitant pathology	33.91±12.08	42.15±11.79	0.001*
*Independent samples t test			

DISCUSSION

In the present study, ankle arthroscopy and posterior ankle endoscopy records of the patients who were operated due to ankle instability were evaluated and an accompanying joint-related pathology was found in 78.2% of the patients. Anterior impingement syndrome and osteochondral defects were found to be the most common accompanying lesions to instability, and the incidence of mentioned lesions increased with age.

It was also found that the mean age of patients with more than one lesion was statistically higher than patients with an additional lesion and patients with an additional lesion than patient without additional lesions. To the best of our knowledge, the present study was the first to investigate the relationship between lesions associated with chronic ankle instability and demographic variables. Also, there was no relationship between gender and variables.

Ankle lesions often coexist and joint-related lesions accompanying chronic ankle instability are common sources of pain and morbidity for patients. Osteochondral lesions, anterior or posterior impingement syndromes and peroneal region problems are common in that group of patients (8).

Anterior ankle impingement can be caused by osteophytes or soft tissue impingement and is clinically seen with limited ankle dorsiflexion and ankle pain. Impingement rates are reported in a wide range in the literature. While osteophytes are present in 11-26% of chronic ankle instability cases, soft tissue compression is observed in 14-82% (9, 10). In the present study, anterior impingement syndrome could be observed in 74.5% of the group, while 83.7% of the patients only had a soft tissue lesion; with 16.3% having both bone and soft tissue impingement pathologies.

The incidence of chondral lesions as a concomitant lesion of ankle instability is reported to be 22-95%, while the incidence of osteochondral lesions is 7-23%. In the present study, osteochondral lesions and chondral degeneration were evaluated and detected in 41.2% and 9.1% of the patients, respectively. The reason for the higher incidence of the osteochondral lesions in our study compared to the percentages reported in the literature could be due to the higher mean age of the patients who were included in the present study (The mean age of Choi et al's study: 27.0, Present Study:38.8) (2, 11).

There were several limitations to the present study due to the retrospective design. The severity of the lesions, the activity levels of the patients, the duration of clinical symptoms and the effect of surgical intervention on clinical outcomes were not evaluated in the present study. Since the evaluation was made only with ankle arthroscopy and posterior ankle endoscopy video recordings, the presence of lesions such as peroneal tendon problems and nerve entrapments outside the examination area could not be evaluated.

In conclusion, the most important finding of the present study was that the presence and number of pathologies accompanying ankle instability were higher with age. Considering the incidence of concomitant lesions in patients to be operated due to chronic ankle instability, a detailed evaluation of preoperative magnetic resonance imaging and performing diagnostic arthroscopy should be beneficial for determining the possible lesions.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the protocol was approved by the ethics committee from the Gazi University (Date:14.07.2020; Decision Number: 07)

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ORIGINAL ARTICLE

Impact of Cardiac Resynchronization Therapy on Indirect Inflammatory Markers

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Abstract

Background: Cardiac resynchronization therapy (CRT) is an established treatment for patients with symptomatic chronic heart failure with reduced ejection fraction (HFrEF) and prolonged QRS despite optimal pharmacological therapy. Inflammation plays a crucial role in the pathogenesis and progression of cardiovascular disease. The role of CRT pre-implantation inflammatory condition assessed using routine laboratory tests has been rarely investigated.

In this study we aimed to evaluate the effect of CRT on indirect inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to- the monocyte (LMR) ratio.

Methods: 75 CRT patients were included in the study retrospectively. Before the CRT implantation, clinical and demographic data were recorded from all patients. NLR, PLR and LMR ratio were measured before CRT implantation. The patients were re-evaluated minimum six months after CRT; the above-mentioned parameters were measured again and compared to the pre-CRT period.

Results: Compared to the period before CRT, laboratory findings such as white blood cell (3.5 ± 2.2 103 uL vs. 3.2 ± 2.4 103 uL; p = 0.006), neutrophyl (1.9 ± 0.4 103 uL; vs. 1.4 ± 0.4 103 uL; p = 0.002), NLR (3.8 ± 0.3 103 uL; vs. 1.7 ± 0.1 103 uL; p <0.001), PLR (490.2 ± 199 103 uL; vs. 381 ± 105 103 uL; p < 0.001) levels were significantly lower after 6 months of CRT implantation. Lymphocyte counts (0.5 ± 0.3 103 uL vs. 0.8 ± 0.2 103 uL; p = 0.001) were significantly higher in the post CRT group. A significant and positive correlation of the reduction in NLR (rs = 0.362, p = 0.001) and PLR (rs = 0.562, p <0.001) was found with the increased six minute walking test (6-MWT).

Conclusion: The NLR, PLR and MLR were decreased after CRT implantation. The modest decrease in these parameters demonstrates the effect of restoring the heart's electromechanical synchrony after CRT on inflammation.

Key Words: Congestive Heart Failure, Cardiac Resynchronization Therapy, İnflammatory Markers.

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INTRODUCTION

Approximately 1–2% of the adult population in developed countries have heart failure (HF), with the prevalence rising to ≥10% among persons 70 years of age or older (1). HF can be classified into three types based on the condition of left ventricular (LV) systolic function: HF with preserved ejection fraction (EF) (EF≥ 50%), mid-range HF (EF:40 - 49 %) and HF with reduced ejection fraction (HFrEF) (EF< 40 %) (2) . Cardiac resynchronization therapy (CRT) is an established treatment for patients with symptomatic chronic HFrEF and prolonged QRS despite optimal pharmacological therapy.

By restoring the heart's electromechanical synchrony, CRT improves self-reported symptoms and reduces mortality and rehospitalization for heart failure (3). Unfortunately, almost a third of patients do not respond favourably to CRT (4). Several characteristics are associated with improved response, and thus survival following CRT implantation (5).

Inflammation plays a crucial role in the pathogenesis and progression of cardiovascular disease. Numerous inflammatory biomarkers are correlated with disease severity and prognosis across throughout HF (6). However, the role of CRT pre-implantation inflammatory condition assessed using routine laboratory tests has been rarely investigated.

In this study we aimed to evaluate the effect of CRT on indirect inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to- the monocyte (LMR) ratio.

MATERIALS AND METHODS

This study was approved by the Ondokuz Mayıs University institutional ethics committee in which it took place in line with the recommendations of the Declaration of Helsinki (Date: 25.02.2016 Decision no: 2016-90).

Study Population and Data Collection

Subjects consisted of 82 consecutive patients undergoing CRT, between January 2017 and December 2019, at Ondokuz Mayıs University School of Medicine Cardiology Department who were retrospectively enrolled into the study. Patients were included according to following criteria: (1) chronic HF with reduced LVEF (≤35%) and (2) prolonged QRS interval (≥130 msn) with LBBB morphology (3) have indication for CRT implantation according to the 2016 European Society of Cardiology guideline for the diagnosis and treatment of acute and chronic HF. CRT implantation was performed to all participants.

Patients with mechanical tricuspid valve, recent myocardial infarction or coronary artery bypass graft surgery (≤ six months), decompensated HF, malignancies, chronic inflammatory disease, haematological disorders, renal or hepatic disorders, right bundle branch block morphology on electrocardiogram (ECG), right ventricular pacing only, pacemaker upgraded to CRT, LV lead inserted into other than lateral or postero-lateral branches of coronary sinus, life expectancy of less than 12 months, and follow-up interval less than six months were excluded from the study. Thus, 7 patients were excluded, and the study cohort included a total of 75 patients. All patients included in the study with either sinus rhythm or atrial fibrillation provided biventricular pacing over 90%.

An independent physician who was blinded to all other data performed the clinical evaluation, including assessment of New York Heart Association (NYHA) class, in all of the patients. QRS duration was measured by surface ECG using the widest QRS complex from the II, V1, and V6 leads. All patients were evaluated in terms of age, gender, coronary artery disease history, diabetes mellitus, hyperlipidaemia, hypertension, and other concomitant diseases. Patients were classified as ischaemic or nonischaemic aetiology of HF. The patients underwent a detailed echocardiographic examination at baseline and six months after the CRT.

Echocardiography

Transthoracic echocardiography (TTE) was performed by an experienced echocardiography specialist who was blinded to other data. Vivid E9 (GE Vingmed Ultrasound, Horten, Norway) TTE device and M5S (1.5-4.5 MHz) ultrasound probe were used for the echocardiographic measurements. Left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), left ventricle end-diastolic (LVEDD) and end-systolic diameters (LVESD), and left atrium (LA) anteroposterior diameter were measured from the long axis view of the heart using TTE. Ejection fraction (EF) was calculated by Modified Simpson method using apical 4-chamber and 2-chamber images. Valvular heart pathologies were detected and graded. Pulmonary arterial pressure was measured.

CRT implantation

Following left pectoral region incision, subclavian venous puncture was performed, and right ventricle and right

atrium leads were placed. After this, coronary sinus was found using a left amplatz catheter, and images were recorded using a contrast-enhancing agent for the selection of the suitable branch. LV lead was placed on the lateral or posterolateral branch of coronary sinus if possible. All electrodes were connected to the generator, and the pouch was closed following stimulus and threshold values were controlled**.** After implantation AV delay of the patients was set to be 120 ms, and VV delay was 0 ms for optimal resynchronization.

Laboratory measurements

In our hospital, blood samples were collected from the antecubital vein within 24 hours of hospital admission. Complete blood cell counts including total white blood cell (WBC), platelet, neutrophil, lymphocyte, and monocyte counts, and haemoglobin level were all measured with an autoanalyzer. NLR was calculated by dividing the neutrophil count by the lymphocyte count. PLR was calculated by dividing the platelet count by the lymphocyte count. LMR was calculated by dividing the lymphocyte count by the monocyte count. Venous blood samples were obtained without venostasis by venepuncture of the large antecubital veins of the patients at least 24 h before CRT implantation and were immediately studied in the laboratory without any time delay. Study patients were re-evaluated minimum 6 months after the CRT implantation and the parameters of pre-CRT and post-CRT periods were compared eachother.

Definitions

Ischemic cardiomyopathy and non-ischemic cardiomyopathy definitions were made based on the presence or absence of myocardial infarction events or 75% or more stenosis in the left coronary artery.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS 22 for Windows (SPSS Inc., Chicago, IL, USA). The continuous variables were tested for a normal distribution using the Kolmogorov–Smirnov test. Normality was checked using the Shapiro–Wilk statistic test. Normally distributed data were presented as the mean ± standard deviation and non-normally distributed data as the median with an interquartile range. The categorical variables were expressed as percentages. A paired sample t test or Wilcoxon's signed-rank test was performed according to the normality of the clinical variables to compare clinical parameters before and six mounth after the CRT. Spearman correlation analysis was used for variables not showing normal distribution. The NYHA class change was compared using Cochran Mantel-Haenszel test for ordered variables. Spearman correlation analysis was performed to examine the relationship between change in NLR, PLR and six-minute walking test (6-MWT). Statistical significance was set at $p < 0.05$.

RESULTS

A total of 75 CRT patients were included in the study. Of the study patients, 54% were males; the mean age was 63.1 ± 12.5 years, and 64% had ischemic etiology. Hypertension was present in 80% of patients. Therapy with beta-blockers and diuretics were at high rates (85.3% vs 96%, respectively). The basic clinical features and laboratory parameters of the study groups are listed in **Table 1**. The echocardiogram and laboratory findings and the clinical parameters evaluated before CRT and after six months are shown in **Table 2**. The heart rate (72.9 ± 4.9 bpm vs 62.8 ± 6.5 bpm, p = 0.002). The LVESV, LVEDV, LVESD and LVEDD decreased significantly ($p < 0.05$). While significant increases occurred in LVEF (30.6 ± 2.9% vs 31.9 ± 2.5%, $p < 0.001$) and the cardiac index (2.3 ± 0.4 L/min/m^2 vs 2.5 ± 0.5 L/min/ m^2, $p < 0.001$), no significant changes were observed in the mitral regurgitation figure (**≥ moderate)** (31 vs 27, p = 0.288)**.** The patients exhibited significant NYHA classes improvement following the initiation of CRT. 6-MWT significantly increased after 6 months of CRT implantation (256 ± 42 vs. 296 ± 52; p=0.002. In their laboratory findings white blood cell (3.5 ± 2.2 10^3 uL vs. 3.2 ± 2.4 10^3 uL; p = 0.006), neutrophyl (1.9 ± 0.4 10^3 uL; vs. 1.4 ± 0.4 10^3 uL; p = 0.002), NLR (3.8 ± 0.3 10^3 uL; vs. 1.7 ± 0.1 10^3 uL; $p < 0.001$), PLR (490.2 ± 199 10^3 uL; vs. 381 ± 105 10^3 uL; $p < 0.001$) levels were significantly lower after 6 months of CRT implantation. Lymphocyte counts (0.5 ± 0.3 10^3 uL vs. 0.8 ± 0.2 10^3 uL; p = 0.001) were significantly higher in the post CRT group. In addition, there was no difference between the groups in terms of other laboratory findings and LMR ($p > 0.05$).

A significant and positive correlation of the reduction in NLR was found with the increased 6-MWT (rs = 0.362, p = 0.001) **(Fig.1A)**. A significant and positive correlation of the reduction in PLR was found with the increased 6-MWT (rs = 0.562, $p < 0.001$) **(Fig.1B)**.

Table 1. Baseline demographic and clinical parameters of the study population

Variable	(n=75)
Age (years)	63.1 ± 12.5
Gender	
Men, n (%)	41 (54.6)
Women, n (%)	34 (45.3)
Body mass index (kg/m²)	22.6 ± 2.6
Smoking	26 (34.6)
Etiology of heart failure	
Ischemic	48 (64)
Non-Ischemic	27 (49)
NYHA class, n (%)	
II	25 (33.3)
III	39 (52)
IV	11 (14.6)
Hypertension, n (%)	60 (80)
Diabetes mellitus, n (%)	28 (37.3)
Atrial fibrillation, n (%)	18 (24)
Beta-blocker, n (%)	64 (85)
ACEI or ARB, n	67 (89)
ARNI, n	5 (6)
Aldosterone receptor blocker, n (%)	51 (68)
Diuretic, n (%)	72 (96)
Ivabradine, n (%)	30 (40)
Digoxin, n (%)	16 (21)
ECG branch block	124.2 ± 9.1
LBBB, n	61 (81.4)
Other bransch blocks, n	14 (18.6)

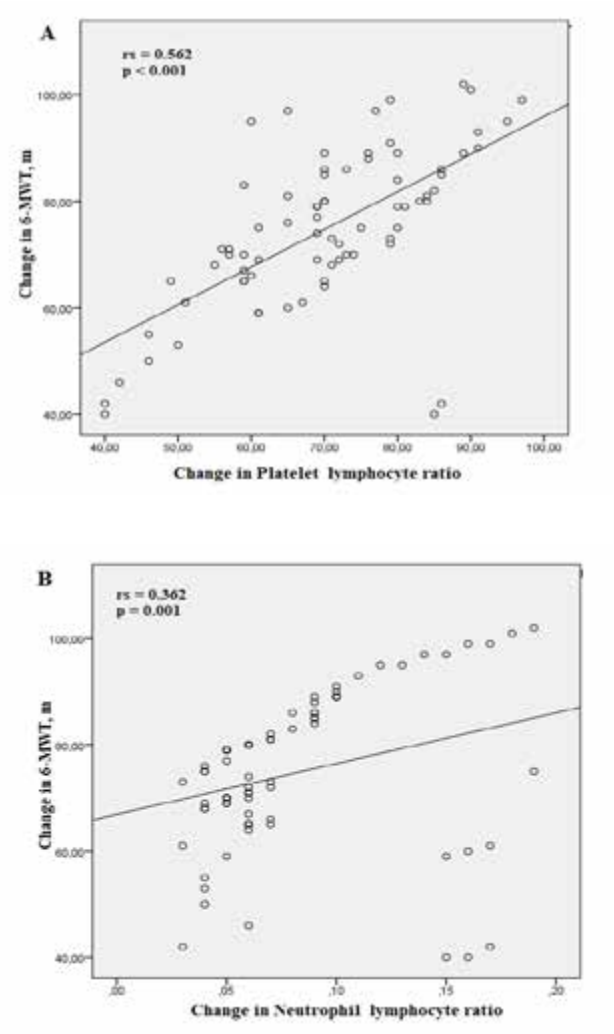
Numerical variables are presented as mean ± SD and categorical variables as percentages. NYHA: New York Heart Association; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ECG: Electrocardiography; LBBB: Left Bundle Branch Block

Table 2. Echocardiographic, laboratory and clinical parameters before and six month after CRT

Parameters	Baseline	6rd month	p value
Heart rate (bpm)	72.9 ± 4.9	62.8 ± 6.5	0.002
QRS duration, msn			
Creatinine, mg/dL	1.01 ± 0.26	1.14 ± 0.28	0.098
Potassium, mEq/L	4.1 ± 0.2	4.4 ± 0.3	0.097
NYHA class			<0.001
I n,(%)	0	3 (4)	
II n,(%)	25 (33.3)	40 (53.3)	
III n,(%)	39 (52)	25 (33.3)	
IV n,(%)	11 (14.6)	7 (9)	
6-MWT, m	256 ± 42	296 ± 52	0.002
White blood cell, 10^3 uL	3.5 ± 2.2	3.2 ± 2.4	0.006
Hemoglobin, g/dL	10.4 ± 2.6	10.8 ± 2.4	0.058
Neutrophil, 10^3 uL	1.9 ± 0.4	1.4 ± 0.4	0.002
Lymphocyte, 10^3 uL	0.5 ± 0.3	0.8 ± 0.2	<0.001
Monocyte, 10^3 uL	0.6 ± 0.3	1 ± 0.2	<0.001
Platelet, 10^3 uL	245 ± 43	305 ± 53	<0.001
NLR	3.8 ± 0.3	1.7 ± 0.1	<0.001
PLR	490 ± 199	381 ± 105	<0.001
LMR	0.8 ± 0.25	0.8 ± 0.21	0.856
LVEDd, mm	58 (56-61)	56 (55-61)	0.017
LVESd, mm	44 (42-47)	41.5 (40-45)	<0.001
LVEF, (%)	30.6 ± 2.9	31.9 ± 2.5	<0.001
LVEDV, mL	161 (146-176)	153.5 (146-167)	0.007
LVESV, mL	114 (100-125)	100 (96-110)	<0.001
Cardiac Index (L/min/m²)	2.3 ± 0.4	2.5 ± 0.5	0.001
Mitral insufficiency (≥ moderate) n, (%)	31 (34)	27 (31.3)	0.288
sPAP, mmHg	33.9 ± 3.7	30.1 ± 2.9	<0.001

Numerical variables are presented as mean± SD and categorical variables as percentages. NYHA: New York Heart Association; 6-MWT: Six month walk test; NLR: neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; LMR: Lymphocyte-monocyte ratio; LV: Left ventricular; EF: Ejection fraction; LVEDd: Left ventricular end-diastolic diameter; LVESd: Left ventricular end-systolic diameter; LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume; sPAB: Systolic pulmonary arterial pressure.

Fig.1 (A) Correlation of change in 6-MWT with PLR. (B) Correlation of change in 6-MWT with change in NLR. rs: indicates correlation coefficient.



DISCUSSION

As a result of our study, we found that CRT causes a moderate decrease in indirect inflammatory parameters. These data suggest that decrease in inflammatory markers of which increased levels are associated with poor outcome in cardiovascular events, important in positive prognostic effects after CRT.

The prevalence of heart failure, especially with the decrease in deaths due to myocardial infarction and sudden cardiac death, is increasing worldwide (1). Endpoints have improved considerably with advances in HF treatment (2).

Cardiac resynchronization therapy, which has a significant contribution to the positive effects, increases cardiac performance in selected eligible patients and provides a significant reduction in symptoms and morbidity and mortality (3). In electrical and mechanical synchronization failure in HF patients, the right and LV leads placed with CRT create two ventricular activation waves that are distributed in opposite directions starting from where they are placed. The beneficial effect of these two depolarization waves is to synchronize the contraction of the LV walls. Thus, the performance of the myocardium, which starts to contract synchronously, increases with both the mechanical effect and the reversing remodelling effect (7).

Heart failure is a systemic condition with increased levels of inflammatory markers. Treatments targeting these pathways have shown a favourable prognostic effect in this syndrome (8).

It is known that the immune system and inflammation play an important role in the pathogenesis of HF. However, the effect of the immunological system on prognosis remains unclear (8). The basis of the interaction between leukocyte derivatives and HF is highly complex (9).

In summary, it has been suggested that systemic cytokine release, which potentially causes lymphocyte apoptosis and activation of the hypothalamic-pituitary-adrenal axis, causes a decrease in % lymphocyte count, especially due to physical stress (8). Previous studies have shown that % lymphocyte count is significantly associated with HF incidence, HF hospitalizations and mortality (10).

Neutrophils play an important role in the inflammation process by producing myeloperoxidase, which promotes phagocytic function. Increased levels of this enzyme also cause excessive free radical production, which has detrimental effects on the myocardium (11). In this context, Avcı and his friends observed a significant negative correlation between NLR and LVEF in patients with idiopathic dilated cardiomyopathy. They found worse functional classes in patients with higher NLR levels in their study and concluded that the higher NLR was useful for evaluating the severity of HF (11). Yıldız and her friends reported higher NLR levels and decreased functional capacity in HFrEF patients with similar LVEF (12). Additionally, Agacdiken and his friends found that the basal NLR is a predictor of the response to CRT (13). Balcı et al., in their study evaluating the response to CRT, found higher NLR and PLR values in patients who did not respond to CRT (14). In our study, a significant decrease in NLR, PLR and MLR was detected in all patient groups after CRT implantation. These results suggest that; the effectiveness of CRT can be demonstrated by using simple inflammatory markers.

This study has some limitations. First, this retrospective study was conducted in a single centre with a small sample size. Second, additional inflammation markers were not assessed to address the other confounding factors. Third the relationship between the inflammatory markers and clinical outcomes were not evaluated. A prospective randomized multi-center study with a larger study population might increase the significance of the presented results.

The NLR, PLR and MLR were decreased after CRT implantation. The modest decrease in these parameters demonstrates the effect of restoring the heart's electromechanical synchrony after CRT on inflamation. These results appeared to be associated with positive response to CRT.

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Declarations

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This study was approved by the Ondokuz Mayıs University institutional ethics committee in which it took place in line with the recommendations of the Declaration of Helsinki (Date: 25.02.2016 Decision no: 2016-90).

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CASE REPORT

Could a Sentinel Lymph Node Biopsy Be Performed with Isolated Methylene Blue Injection in a Patient with a History of Skin-Sparing Mastectomy and Prosthetic Reconstruction?

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Abstract

Evaluation of lymphatic spread in early stage breast cancer without clinical and radiological evidence of metastasis can be performed by sentinel lymph node biopsy (SLNB). However, controversies about performing the SLNB in patients who have a history of major breast or axillary region surgery keep going. This case report presents the outcomes of a SLNB performed on a 42-year-old woman who had been previously treated with bilateral nipple and skin-sparing mastectomy and breast reconstruction with areolar complex transfer and silicone breast implants. 0.5% diluted methylene blue solution was injected intradermally as a marker. SLNB is an inexpensive and effective method for adequate axillary evaluation in cases with previous mastectomy history. Intradermal injection of 0.5% diluted methylene blue could reduce the risk of skin necrosis and breast prosthesis rupture.

Key words: Sentinel Lymph Node Biopsy, Breast Cancer, Methylene Blue, Previous Skin-Sparing Mastectomy.

INTRODUCTION

Sentinel lymph node biopsy (SLNB) is the standard assessment method of the lymphatic system used in early-stage (T1 or T2) breast cancer patients when axillary lymph nodes are clinically negative (1). If there is no evidence of malignancy in the SLNB of patients undergoing surgery due to breast cancer, then axillary lymph node dissection (ALND), which causes high morbidity, may not be performed (2). Methylene blue, isosulfan blue and radioisotope materials could be used in SLNB for marking lymphatic tissue (3). After an excisional biopsy of breast tumors, it is reported that SLNB is an appropriate technique for determining the lymphoid metastases (4). However, performing SLNB in patients who have previously undergone major breast or axilla surgery is still controversial (5, 6).

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This case report aims to present the results of performing SLNB by using intradermal methylene blue on a 42-year-old woman who had been previously treated with bilateral nipple and skin-sparing mastectomy and breast reconstruction.

CASE REPORT

A 42-year-old woman in the premenopausal period who had no family history of breast cancer revealed lesions that were radiologically typed as BIRADS 3 in the left breast during malignancy screening. It was noticed that the patient gave birth twice and continued to breastfeed after both pregnancies for two years. After an evaluation performed at the plastic surgery clinic for breast masses, a bilateral skin and areola sparing mastectomy was performed. Breast reconstruction was added to the procedure by using pre-pectoral implants. In the pathological evaluation, a solid lesion was detected at the upper left part of the left breast, and the largest diameter of the tumor was 9 mm. Surgical margins at the anterior, posterior, and lateral sides were 1, 5, and 10 mm, respectively. As a result of the histological evaluation, the patient was diagnosed with invasive ductal carcinoma.

No axillary involvement was detected by ultrasonography and PET/CT evaluations. The patient was referred to a general surgery outpatient clinic after evaluation of the pathological examination results. The multidisciplinary oncology council concluded that the clinical and radiological evaluation of the axillary lymph node area of the patient was not sufficient due to the pathological diagnosis. Axillary lymph node dissection may cause many morbidities, especially lymphedema and nerve injuries in the arm. In order to avoid the morbidity of ALND, SLNB was planned as the first procedure to evaluate the lymphatic system for the extent of ductal carcinoma invasion.

Since the entire breast parenchyma had been excised, the methylene blue solution was diluted due to the fact that a 1% solution could cause necrosis on the skin. The 0.5% methylene blue solution was injected equally into each periareolar quadrant intradermally. In order to facilitate the transition of the injected solution to the lymphatic system, gentle breast massage was performed from the areola towards the axilla for five minutes.

The axillary region was exposed by using an incision parallel to the lateral margin of the pectoralis major muscle in order to reach the sentinel lymph node region. Blue stained lymphatics were found and the blue lymph nodes were excised after the clavipectoral fascia was dissected (Figure 1). Histopathological evaluation revealed that none of the sentinel lymph nodes were positive for malignancy involvement (Figure 2). There was no hyperemia, ischemia, or necrosis on the skin during the postoperative follow-up (Figures 3 and 4). The patient was referred to the radiation oncology clinic for entire breast and axilla radiotherapy.

Figure 1: axillery incision after the blue lymph nodes were excised

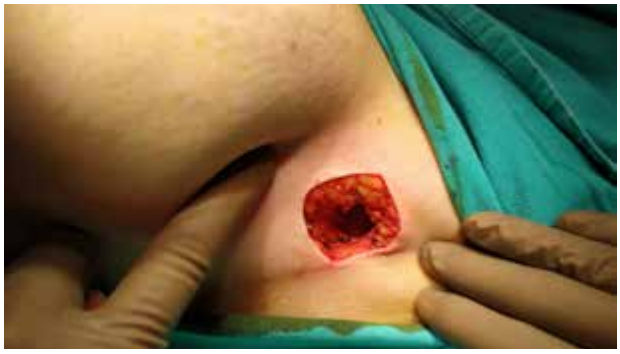


Figure 2: the surgical specimen

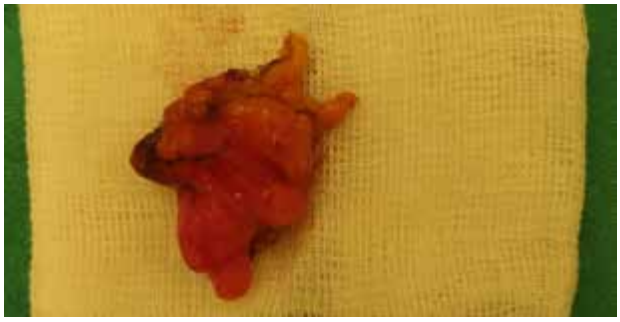


Figure 3: There was no hyperemia, ischemia or necrosis after the operation.

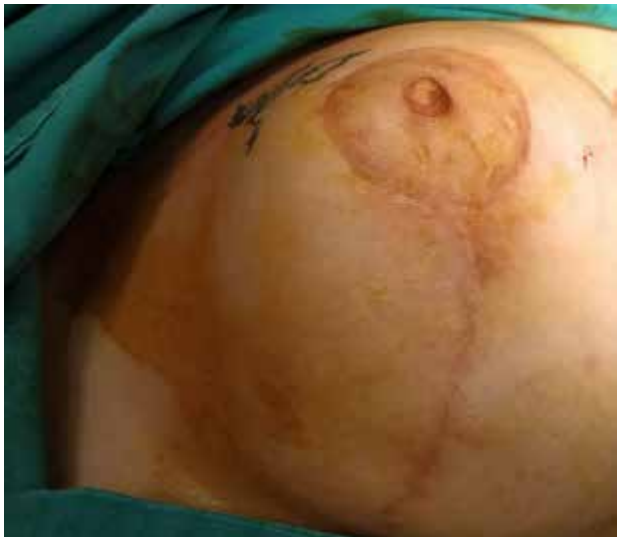
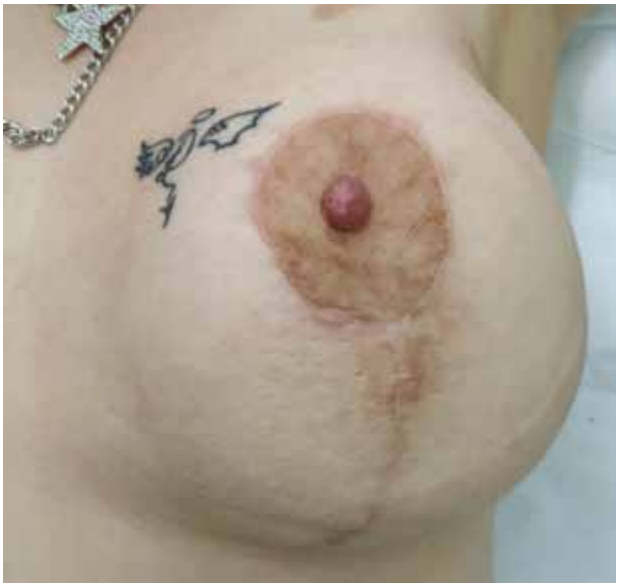


Figure 4: There was no hyperemia, ischemia or necrosis after 2 mounts.



DISCUSSION

SLNB is based on the theory that lymphatic flow in the breast goes directly to a single lymph node in the axilla. Therefore, it is controversial to perform SLNB in patients who have previously undergone breast or axilla surgery. The reliability of SLNB after an incisional biopsy in the breast was investigated by Çelebioğlu et al., and recognition of the sentinel lymph nodes and false negativity rates are reported similar to primary excisions (4). In patients who have previously undergone breast and axilla surgery, the recognition ratio of the sentinel lymph node in SLNB is approximately 60%, and there is still benefit in performing it. However, because the lymphatic drainage pattern is likely to change, doing it together with lymphoscintigraphy could decrease the false negativity rate (5, 7). Despite this, a lymphoscintigraphy and gamma probe could not be performed on the current patient due to changing hospital conditions during the COVID-19 pandemic. In addition, the value of subsequent SLNB is not clear in patients undergoing cosmetic breast surgery (reduction mammoplasty, breast augmentation) (8–10).

In the current case, axillary surgery was not performed, but the breast parenchyma was completely excised. In a study by Karam et al., 20 patients who had previously undergone mastectomy underwent SLNB due to recurrence. Sentinel lymph nodes were identified in 13 of them. In the aforementioned study, a radioisotope was used in each patient as a marker, and blue dye was added in some of the patients (11). In another study by Intra et al, SLNB was performed on four patients who had previously undergone mastectomy without axillary surgery due to ductal carcinoma in situ (DCIS). Sentinel lymph nodes were identified in all of four patients, and ALND was performed on two of them due to positive results from the SLNB. In this study, radioisotopes were used as markers, and blue dyes were not used (12). In the case presented by Vicente et al, SLNB was performed using radioisotopes and isosulfan blue as markers on a patient who underwent mastectomy five years previously due to DCIS. The operation was completed with ALND, since all three lymph nodes that were removed were positive (13).

In the literature, radioisotope substances have frequently been used as markers in SLNB after mastectomy. It has also been reported in the literature that skin necrosis may develop due to intradermal administration of methylene blue (14).

In the current case, sentinel lymph nodes were diagnosed with only intradermal methylene blue injection without using any radioisotopes. During the procedure or follow-up period, there were no complications related to the skin or breast implant because methylene blue was administered intradermally at a lower dilution (0.5%).

SLNB with intradermal injection of 0.5% isolated methylene blue solution is an easy, practical, inexpensive, and effective alternative technique that could be performed on patients with a history of mastectomy in specialized centers on oncological surgery.

Declarations

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CASE REPORT

Giant Median Lobe Hyperplasia of the Prostate Mimicking Bladder Tumor: A Case Report

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Abstract

Benign prostatic hyperplasia is a common cause of bladder outlet obstruction and may cause macroscopic hematuria. Giant median lobe hyperplasia is very rare and its definition is not clear. In this case report, the diagnosis and treatment of a case with giant median lobe hyperplasia of the prostate mimicking a bladder tumor were evaluated. A 65-year-old male patient was admitted to our clinic with a 9-month history of intermittent hematuria. Abdominopelvic computed tomography revealed a mass measuring 95x85x57 mm filling the bladder. A distinct anatomical plane between the mass and the seminal vesicles could not be identified. In the urethrocystoscopy, it was determined that the mass was the giant median lobe of the prostate. Open suprapubic prostatectomy was performed. A total of 330 g prostate tissue consisting of 180 g median lobe was enucleated. Giant median lobe hyperplasia of the prostate is a rare pathology and may mimic a bladder tumor by causing painless hematuria.

Key words: Giant Prostatic Hyperplasia, Case Report, Suprapubic Open Prostatectomy.

INTRODUCTION

Benign prostate hyperplasia (BPH) is histologically defined as oblong hyperplastic tissue nodules, most often composed of epithelium and stroma. (1). The prostate gland due to BPH can sometimes be very large. Giant prostatic hyperplasia is a rare condition characterized by a BPH weighing more than 500 g (2). In most of the cases reported in the literature, the prostate is often overgrown by lateral lobes (3). In the literature, the giant median lobe hyperplasia of the prostate is very rare and its definition is not clear. In this case report, the diagnosis and treatment of a case with giant median lobe hyperplasia of the prostate mimicking a bladder tumor was evaluated.

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CASE REPORT

A 65-year-old male patient presented to our clinic with intermittent painless hematuria ongoing for 9 months in January 2018. He had no voiding symptoms. He had a history of transurethral resection of the prostate due to BPH in 2010 and 2015 and prostate biopsy due to high level of serum prostate-specific antigen (PSA) in 2016 (16 ng / dL) (pathology benign). Physical examination was normal. Digital examination revealed a large but benign and non-nodular prostate. Chest x-ray, hemogram and serum biochemistry were normal. Serum PSA level was 21 ng / ml. Abdominopelvic computed tomography showed a contrasting mass measured 95x85x57 mm occupying the whole bladder (Figure 1). A distinct anatomical plane between the mass and the seminal vesicles could not be identified. An urethrocystoscopy was performed and it was determined that the mass defined in the tomography was the giant median lobe of the prostate. The patient underwent open suprapubic prostatectomy surgery. A total of 330 g prostate tissue including 180 g median lobe was enucleated. The amount of peri-operative bleeding was approximately 350 cc. Postoperative biochemistry and hemogram values were normal. The patient was discharged on the postoperative 7th day. Pathological examination of the surgical specimen was reported as nodular hyperplasia.

Figure-1: a) The mass completely filling the bladder b) Lateral lobes of the prostate

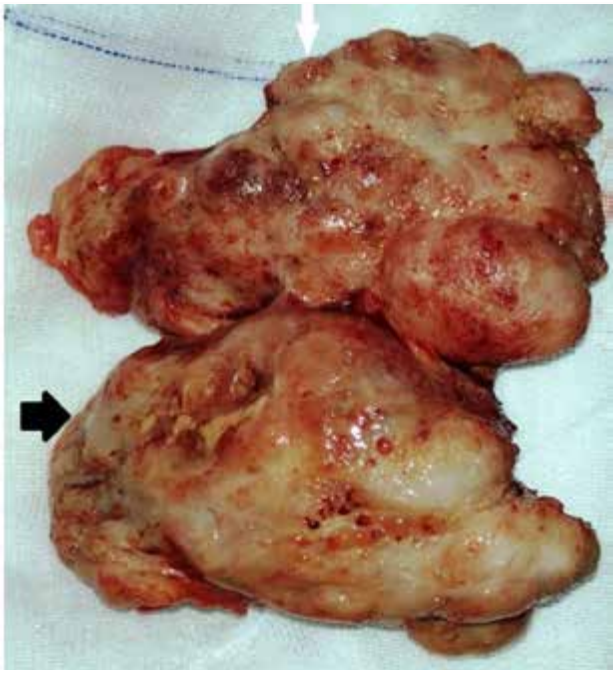
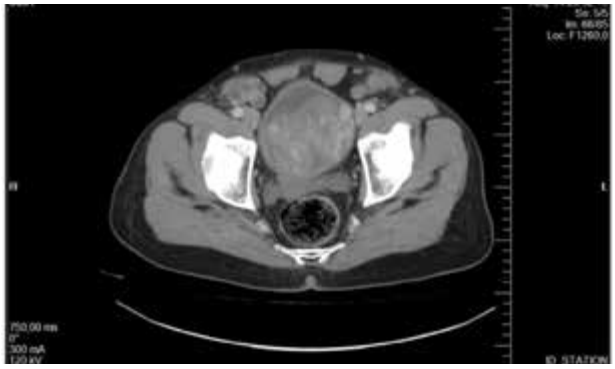
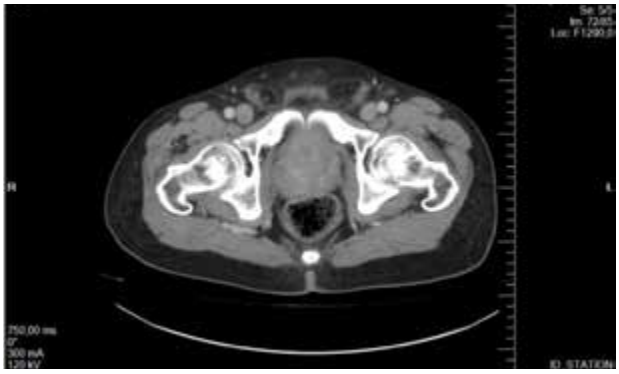


Figure-2: Prostate tissue consisting of enucleated median (marked with white arrow) and lateral lobes (marked with black arrow).

a)



b)



DISCUSSION

Benign prostatic hyperplasia is a common cause of bladder outlet obstruction and may cause macroscopic hematuria. It is one of the most common diseases in aging men and 60% of 60-year-old male patients have BPH histologically (4).

Prostates weighing more than 500 g are defined as 'giant prostate hyperplasias' (5). In the literature, more than 20 giant prostatic hyperplasia cases have been reported and giant median lobe is quite rare (6). Although there is no specific definition for giant prostate median lobe hyperplasia in the English literature, Ibrahim AG et al. presented a BPH case called "Giant median lobe enlargement of the prostate mimicking advanced bladder tumour: a case report" in 2014 with 225 g median lobe mimicking a bladder tumor (7). Our case was a BPH case with 180 g median lobe mimicking a bladder tumor.

Gross hematuria is not a common symptom for patients presenting for the first time. Macroscopic hematuria is observed in 2.5% of patients with BPH according to previous studies (8). Although the etiology of hematuria is not clear in these patients, the increased microvascular density of the prostate or the increased release of vascular endothelial growth factor may be the reasons causing hematuria (9). Because the patient had hematuria and the computed tomography revealed a mass filling the bladder, our provisional diagnosis was a bladder tumor.

Acute or chronic urinary retention, recurrent gross hematuria, urinary tract infection, renal failure, bladder stones and presence of lower urinary tract symptoms resistant to serious medical treatment are indications for surgical treatment. Transurethral prostate resection transurethral prostate incision laser vaporization and enucleation techniques are surgical options for small and mid-sized prostates (4). Although minimally invasive methods have been described, open prostatectomy is still the gold standard procedure for prostates with greater volume (>80 gr) (10). Suprapubic prostatectomy is the enucleation of the prostatic adenoma with an extraperitoneal incision of the lower anterior wall of the bladder. It is preferred especially in cases with a large median lobe (11). In our case, open suprapubic prostatectomy procedure was performed.

Giant median lobe hyperplasia of the prostate is a rare pathology and may mimic bladder tumors by causing painless hematuria. Differential diagnosis is important in shaping the treatment since its symptoms are similar to a bladder tumor.

Declarations

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