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The Journal of Pediatric Academy is the official publication of the Kayseri Children Health Association. The Journal of Pediatric Academy is an international, peer-reviewed, open-access electronic and conventional published journal in the English language. The Journal of Pediatric Academy is publishing as 3 issues per year (April, August, and December). The journal accepts original research articles, invited review articles, clinical reports, and case reports in all areas of pediatric research, which summarize recent developments about a particular subject based on standards of excellence and expertise.

Information About the Journal

J. Pediatr. Acad. (JPA) was established in 2020 as open access and peer-reviewed journal that accepts articles in English. J. Pediatr. Acad. (JPA) is published 3 times a year. Articles submitted should not have been previously published or be currently under consideration for publication any place else and should report original unpublished research results. The journal does not expect any fees for publication. All articles are available on the website of the journal for all readers.

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Journal of Pediatric Academy (JPA) reports on major advances in the diagnosis and treatment of diseases in children. Each issue presents informative original research articles, review articles, case reports, image corners, and letters to the editor from leading clinicians and investigators worldwide.

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A submitted manuscript must be an original contribution not previously published (except as an abstract or a preliminary report), must not be under consideration for publication elsewhere, and, if accepted, must not be published elsewhere in a similar form, in any language. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the Journal, its editors, or the publisher. All manuscripts must be submitted on-line through the journal's Web site at https://www.jpediatricacademy.com/index.php/jpa

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Text: Organize the manuscript into four main headings: Introduction, Materials and Methods, Results, and Discussion. Define abbreviations at first mention in the text and each table and figure. If a brand name is cited, supply the manufacturer's name and address (city and state/country). All forms of support, including pharmaceutical industry support, must be acknowledged in the Acknowledgment section.

Abbreviations: For a list of standard abbreviations, consult the Council of Biology Editors Style Guide (available from the Council of Science Editors, 9650 Rockville Pike, Bethesda, MD 20814) or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure.

Manuscript Types

JPA publishes the types of articles briefly described below.

Editorial Comment:

Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with a high reputation on the topic of the research article published in the journal. The authors are selected and invited by the journal to provide such comments. The text should contain 1500 words or fewer. it includes 5 figures and/or tables or fewer and 15 references or fewer.

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

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Units should be prepared by the International System of Units (SI).

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Clinical observations may include case histories that demonstrate novel findings or associations, important clinical responses when a larger study is not needed to address a specific issue, or a unique laboratory observation linked to clinical care and/or practice. The text should contain 1500 words or fewer, with a brief abstract of 200 words or fewer. Abstracts outline background, observation(s), and conclusions. Include 5 figures and/or tables or fewer and 15 references or fewer.

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For educational purposes, the journal publishes original, interesting, and high-quality clinical images having a brief explanation (maximum 500 words excluding references but including figure legends) and of educational significance. The figure legend should contain no more than 100 words. It can be signed by no more than 5 authors and can have no more than 5 references and 3 figures or tables. Any information that might identify the patient or hospital, including the date, should be removed from the image. An abstract is not required with this type of manuscripts. The main text of clinical images should be structured with the following subheadings: Case, and References.

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Letters to the editor should pertain to articles published within the Journal of Pediatric Academy or highlight important new clinical or laboratory insights. The text should contain 1000 words or fewer.

Table 1
Limitations for each manuscript type

Manuscript Type	Word Limit	Abstract Word Limit	Reference Limit	Table Limit	Figure Limit
Editorial comment	1500	No abstract	15	2	5
Original Article	3500	300	50	6	6
Invited Review	5000	350	100	6	10
Case Report	1500	200	15	2	5
Image corner	500	No abstract	5	-	3
Letter to the Editor	1000	No abstract	5	1	1

References:

The authors are responsible for the accuracy of the references. Key the references (double-spaced) at the end of the manuscript. Cite the references in the text in the order of appearance. Cite unpublished data—such as papers submitted but not yet accepted for publication and personal communications, including e-mail communications—in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/tsd/serials/lji.html. Sample references are given below:

Journal Article:

1. Ang KK, Price RE, Stephens LC, et al. The tolerance of primate spinal cord to re-irradiation. *Int J Radiat Oncol Biol Phys*. 1993;25:459–464.

Journal Article published in non-English Languages:

2. Altuntaş N, Çelebi DT, Koçak M, Andıran N. Yenidoğan bebeklerde direkt coombs testi taraması ve pozitifliğinin morbidite üzerine, etkisi; tek merkezd eneyimi. *Pam Tip Derg* 2015;8:39-44. (in Turkish)

Book Chapter:

3. Dimery IW. Chemotherapy in head and neck cancer. In: Myerhoff WI, Rice DH, eds. Otolaryngology: head and neck surgery, 2nd ed. Philadelphia: WB Saunders, 1992:1027–1045.

Entire Book:

4. Virchow R. Cellular Pathology. Philadelphia: JB Lippincott, 1863.

Software:

5. Epi Info [computer program]. Version 6. Atlanta, GA: Centers for Disease Control and Prevention; 1994.

Online Journals:

6. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database:

7. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web:

8. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS Web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

URL (Uniform Resource Locator)

9. (J. M. Kramer, K. Kramer [jmkramer@umich.edu], e-mail, March 6, 1996).

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4. Each reference cited in the text should be listed in the References section.

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Invited Review

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Digital Media and Children

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Abstract

Today, digital media occupies an important place in human life and children live in this technological environment. Exposure to excessive and inappropriate digital media content, especially in early childhood, when brain development is important, has negative effects both in childhood and adulthood. Excessive and poor quality digital media use has been found to be associated with early effects such as sleep problems, negative self-regulation skills, cyberbullying, psychological disorders, and adult diseases such as obesity and cardiovascular disease. In the light of these data, the American Academy of Pediatrics does not recommend screen use for children before 18 months, except for video chat. It is important for parents to choose quality content in the use of digital media, to be a role model for their children, to guide them and to keep in touch with their children while using the screen.

Keywords: Children, digital media, internet use

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Introduction

At the beginning of the most important technological developments that left their mark on the 20th century, traditional media tools such as television and radio and the internet, which is a product of new technological developments, come to the service of societies. The "Information Age", which started with technological developments, provides an environment for communication, socialization, education and learning with the introduction of the internet into our lives. While there were approximately 3.6 billion social media users worldwide in 2020, this number is expected to increase to approximately 4.41 billion in 2025[1]. Digital environments, which have a large place in the life of modern people, also affect children, and today's children are born into this new technological environment. The attitudes of parents in their use of digital media and the limits they set for their children also affect the age and severity of children's exposure to digital media. The use of interactive social media should be considered especially in terms of risks in childhood, especially in the young age group with critical brain development. As a result of the ubiquity of digital media, it has been determined that children spend an average of more than 2 hours a day on digital media[2]. The World Health Organization also draws attention to the fact that children spend most of their time with technology, emphasizing that excessive and problematic use of technology can be a public health problem, and recommends that the time spent by young children in front of the screen should be limited to a maximum of 1 hour a day[3].

Highlights

- Due to internet being easily and uncontrollably accessible, it may have negative effects especially in early childhood with critical brain development.
- Excessive and uncontrolled internet use has negative social, psychological, physical and developmental effects such as sleep problems, negative eating habits, self-regulation, developing internet addiction, cyber bullying, depression, and anxiety.
- In the digital age that today's children are born into, it is important to use high quality applications suitable for interactive age under parental supervision and to guide children on security and privacy issues.

Effects of Digital Media

Although interactive social media can encourage interaction with peers with similar interests and facilitate communication and information exchange, the fact that the internet is easily and uncontrollably accessible due to its nature can negatively affect exposure to cyberbullying, sleep patterns and body image perception for the children who have not yet completed their psychosocial development. It can also facilitate access and transmission of harmful content, which can result in increased stress and anxiety. and cause retardation in cognitive skills, eye problems and metabolic diseases.[4,5]

High-quality television content has been shown to positively affect learning, social and emotional skills in preschool children. Children under the age of three can learn vocabulary through video when certain conditions are met, such as non-verbal communication such as the caregiver's gaze and facial expressions, and interactive verbal communication.[6] On the other hand, symbolic, memory and attention skills are not sufficiently developed in children younger than 15 months. Thus, they can not comprehend the information they learned through the screen in three dimensions, learning occurs by memorization.[7] They can not interact with the image, especially in the use of traditional media such as television. Using well-designed educational apps on mobile phones can help school-age children reinforce what they've learned.[8] However, the fact that most apps are also designed for adults offers only a rote approach.[8] Early and adequate child care interaction contributes to behavioral and neurocognitive system development. Eye contact or joint visual attention between child and caregiver is associated with self-regulation and healthy attachment. In an environment where parents use television and mobile devices in the background, attention shifts away from parent-child interaction, causing less verbal and nonverbal interaction and parent-child conflict.[9,10] Thus, the use of quality interactive media should be supported, especially under the guidance of parents of young children.

Language development is one of the strongest indicators of academic success.[11] Studies show that greater television exposure among young children is linked to poor language development.[12] In a study involving 6-24 month-old children in the USA, it was found that parental mobile device use and children's exposure to television were associated with an increase in average daily mobile device use and expressive language delay in children.[13]

Self-regulation is the conscious management of emotions, thoughts and behaviors.[14] While the use of interactive quality digital media under parental supervision affects the learning and development of the child positively, excessive and uncontrolled media use may negatively affect the positive discipline practices and the development of children's self-control skills. Studies also show the effects of digital media use on self-control. In a study involving preschool children, a relationship was found between more tablet use and poor self-regulation.[15] In another study, it was found that preschool children who spent more than 30 minutes a day on mobile applications had lower self-regulation scores.[16]

Use of problematic social media can lead to body dissatisfaction and a tendency to perceive oneself as overweight.[17,18] A study among adolescents in Italy and the USA showed that internet addiction was significantly associated with low self-esteem and decreased life satisfaction.[19] Internet addiction, which was first defined in the 90s, is defined as the situation in which an individual loses control of his/her internet use and continues to use the internet excessively and encounters problematic consequences that negatively affect his/her life.[20,21]

According to Young, the diagnostic criterias for internet addiction are:[22]

- Excessive mental preoccupation with the internet (constantly thinking about the internet, daydreaming about the activities done on the internet, thinking about the next activity planned to be done on the internet, etc.)
- Needing to use the internet more and more to get the desired enjoyment
- Unsuccessful attempts to control, reduce or completely quit internet use
- Feeling restless, depressed or angry in case of reducing or completely stopping internet use
- Staying on the internet for longer than originally planned, Family, school, work and stress due to excessive internet use
- Having problems with friends, jeopardizing or losing an educational or career opportunity
- Lying to others (family, friends, therapist, etc.) about the time spent on the Internet,
- Using the Internet to avoid problems or experience negative emotions (e.g., helplessness, guilt, depression, anxiety).

Internet addiction is significantly associated with psychological and interpersonal problems such as inability to relate to other people, loss of control over one's own behavior, withdrawal from social activities, difficulty in maintaining a regular schedule, sleep disturbance and decreased sleep, social withdrawal, loneliness, low motivation and low educational performance in adolescents.[23,24] In a study involving European countries, the risk of internet addiction in 9th and 10th grade students was found to be between 0.8% and 1.7%25. In a meta-analysis, global internet addiction was found to be 6%.[26]

It has been reported that excessive and uncontrolled use of digital devices is associated with negative health outcomes such as psychological problems, low emotional stability, depression, anxiety, symptoms of attention deficit, deterioration in emotional and social intelligence, and risk of social isolation.[27] In a study, it was shown that there is a relationship between intense social media/internet use and increased suicide attempts.[28] In a cohort study of 6595 people, adolescents who spent more than 3 hours per day using social media were found to be at high risk for mental health problems, especially internalization problems.[29] Another study revealed that the younger generation, known as “iGen,” born into digital environment after 1995, is more likely to experience mental health problems than their peers (millennial predecessors).[30]

Early childhood is a period in which food preferences and taste are shaped and healthy eating habits are acquired.[31] New technological and other traditional media tools, which are open to uncontrolled access, can cause children to be exposed to food advertisements in an uncontrolled way, causing them to acquire poor eating habits, associated with metabolic diseases such as diabetes and obesity in adulthood.[32] Studies show that food advertisements in digital media affect children's dietary preferences and eating habits.[33,34]

Children who spend longer hours in front of a screen are more likely to experience sleep problems, as the screen is preferred over sleep and the blue light emitted from the screen can delay melatonin production and sleep.[35,36] A study conducted in the USA reported that children who did at least 60 minutes of physical activity a day, slept between 9 and 11 hours a night, and had two hours or less screen use had higher cognitive levels.[37]

Cyberbullying can be defined as the deliberate use of information and communication technologies such as electronic mail, smart phone, short message services, gaming and social media platforms, carried out repeatedly by a group or individual to support deliberate, repetitive and hostile behavior against an individual including spreading lies, posting embarrassing photos or videos, sending hurtful, abusive or threatening messages, images or videos, impersonating someone and sending mean messages to others on their behalf or through fake accounts.[38] As content is quickly shared and disseminated online, the victim may experience a lack of control, as well as a range of highly negative psychological consequences over time, such as social anxiety, depression, and suicidal ideas and attempt, especially when bullying behavior continues.[39] A 2018 study on the mental health of children and youth in the UK found that one in five children aged 11 to 19 had been cyberbullied (21.2%).[40] In another study conducted in England and involving 100,000 adolescents aged 15 years, 42% of the participants reported that they had experienced cyberbullying.[41]

In addition to its systemic effects, COVID-19 also affects all people of the world physically and mentally.[42] During the pandemic, schoolchildren's isolation at home and the use of the internet for education/training, socializing and leisure activities have increased their risk of being exposed to online activities more than before during the COVID- 19 pandemic. According to studies, internet use has increased by 50-70% in some parts of the world following the spread of COVID-19, as the introduction of distance education provides opportunities for children to connect and play with friends, parents and relatives while in isolation.[43]

Digital environments can support online social development, social bonding with peers, and communication with family members at a distance.[44] Especially in adolescents, it can be used as an escape form to cope with low mood and difficult thoughts and to adapt to a new situation.[45] On the other hand, the social, intellectual and self-regulation skills of young children who are introduced to social media that are not designed for them and have limited preparations are at risk during the COVID-19 outbreak compared to children over 13 who have more digital media experience.[46] While media use is used as a coping strategy, it may be harmful for individuals at risk for addictive behaviors or psychological distress.[47] The World Health Organization and UNICEF draw attention to the fact that the COVID-19 pandemic may adversely affect the well-being of children and adolescents, especially with the effect of increasing media use.[48] A study of parents found that it is more difficult to control children's screen time during the COVID-19 pandemic, and nearly half of parents with

children aged 5-15 are forced to relax some rules about what their children do online in 2020. Increased online activity supports children to learn, socialize and play, but also puts them at higher risk. Increased use of the Internet can put children at greater risk for online harm, such as sexual exploitation and cyberbullying.[43]

During the pandemic, it is important for parents to stay in touch with their children's friends, interact with their children through video games and online experiences, and encourage their children to stay physically active in front of screens.[49] During the pandemic, parents can regulate children's media use by watching digital media with their children and explaining or guiding them what they see.[50]

Parental Tips

In a world where children "grow digitally", parents play an important role in teaching them how to use technology safely. Parents should follow age-appropriate apps, games, and programs for their children. The use of media devices should be by communicating with the child under parental guidance to encourage the child's learning and interactions. Families should monitor children's media content and apps used or downloaded.[51] Parents become role models for their children with their attitudes to use digital devices and social media. Media-focused parents are more likely to have children who use more media.[52] These parents are also less likely to respond to their children's requests for attention, and on the other hand, children may exhibit more attention-grabbing behavior.[53] The fact that parents regularly use digital cameras, mobile phones and tablets to take images and videos of their children and show the resulting image to the child on their digital devices causes children to accept the digital environment without limits and makes it difficult to set rules. A parent's use of screen media as an editing tool or a virtual "babysitter", giving the child a sedative or a device to keep them busy, will reinforce the continuation of problematic media use.[54]

Since the use of digital media has become an ordinary part of life, especially including risk factors for children, and parents' attitudes and boundaries play an important role in children's use of digital media, the American Academy of Pediatrics has made recommendations:[7]

- Avoid media use except video chat for children 18 months and younger
- For children aged 18 to 24 months, use high-quality media with their parents to help their children comprehend what they watch.
- For children aged 2 to 5, watching high-quality programs under parental control should not be more than 1 hour per day
- For school children, media should not be allowed to take the place of other important activities such as quality sleep, regular exercise and family meals.

Recommendations to families for their children's use of digital media can be listed as follows:[7,51]

- Avoiding using screen media other than video chat for children 18 months and younger
- Use of high quality media for 18 to 24 month old children with parents to help their children understand what they see
- Not watching high quality programs under parental control for more than 1 hour a day for children aged 2 to 5, and no more than 2 hours a day for children aged 5 to 8
- Not using social media before the age of 13
- Not using digital media during meals
- Ending screen use at least 1 hour before bedtime
- When using the screen, the child should be in contact, the children's understanding of the media content should be supported, not only verbal communication, but also non-verbal communication such as smiling and eye contact should be used.
- Children should be guided in learning to decide and evaluate what is “good” or “right” for them.
- Allow children to explore the media and compare social settings
- The child should be guided on issues such as privacy and security when using digital media resources

Digital media is an environment that takes place in the lives of today's children, which has psychological, social and physical consequences when excessive and uncontrolled use, and where families can protect them from risks by staying in touch with their children and using quality applications. In child health follow-up visits, it is important that pediatricians give advice to families about the use of digital media and answer their questions.

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Invited Review

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Musculoskeletal Complaints: When Should We Consult a Pediatric Rheumatologist?

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Abstract

This review aimed to summarize key points that might suggest rheumatologic diseases to physicians dealing with musculoskeletal (MSK) complaints. Evaluation of a child presenting with MSK findings requires a comprehensive, multidisciplinary, and systematic approach. In children with MSK complaints, detailed anamnesis, appropriate physical examination and joint examination, and the use of correct laboratory tests will be helpful for accurate diagnosis. The algorithm we have suggested for MSK complaints of children will be a guide for the physicians.

Keywords: Musculoskeletal complaints, joint pain, rheumatology, juvenile idiopathic arthritis

Introduction

Musculoskeletal (MSK) features account for 10%–20% of pediatric patients' complaints in primary care clinics.[1] It was shown that approximately 50% of the children and adolescents present with MSK complaints at least once during any period of their life.[1] The underlying causes are highly variable, ranging from benign muscular conditions to rheumatic diseases or malignancies. For instance, constitutional symptoms such as the presence of fever and fatigue, nature and location of pain, duration of morning stiffness, and presence of abnormal examination findings may be helpful while finding out the underlying etiology. Some 'red flags' may guide the clinicians while making the differential diagnosis. A large number of patients with joint pain, fever of unknown origin, elevated acute phase reactants (APRs) and positive anti-nuclear antibody (ANA) are generally referred to a pediatric rheumatologist. However, underlying aetiologies are often found to be infectious, orthopedic, or traumatic conditions that can be recognized by a pediatrician.[2] Pediatric rheumatology has emerged as a subspecialty of pediatrics in the last 50 years

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and then fellow education programs have been started all around the world. However, due to the insufficient number of specialists or centers in rural areas, patients still face problems when accessing appropriate care. Previous studies demonstrated that only half of the patients referred to rheumatology centers were finally diagnosed with rheumatic disease.[3-5] Improvement in the awareness of rheumatic diseases, as well as their differential diagnosis, will alleviate unnecessary consultations and lead to effective utilization of the capacity of pediatric rheumatologists. This review was organized to reveal key points that might suggest rheumatologic diseases to physicians dealing with musculoskeletal complaints.

Highlights

- Nature, location, duration, and timing of pain, accompanying systemic and dermatologic features may concern important clues.
- Inflammatory joint pain usually occurs in the morning after a long period of immobility.
- Mechanical joint pain is more likely to worsen with exercise.

History Taking

A proper anamnesis and a detailed physical examination contain many clues that will lead us to the correct diagnosis. 'Listen to your patient; they are telling you the diagnosis' is a well-known and much-quoted aphorism. Nature, location, duration, and timing of pain, accompanying systemic and dermatologic features, exacerbating or relieving factors of complaints, family history of autoimmune or auto-inflammatory diseases usually concern important clues leading clinicians to make an accurate diagnosis while assessing children with MSK complaints. Since children are not just 'little adults', the assessment and management of children with MSK complaints require a special approach. It is difficult for younger children to define the location and character of pain, both because of the reflected pain and incomplete language development in early childhood. These points may cause family anxiety and may also make it complicated for the clinicians to make a differential diagnosis. Segal et al.6 designed a decision support software to reduce diagnostic errors in pediatric rheumatology practice (www.simulconsult.com). Using such special software or following the clues for the diagnosis will greatly reduce unnecessary consultations (**Figure 1**). The differential diagnoses of MSK complaints are depicted in **Table 1**.

With detailed anamnesis by taking into account the clues and with appropriate physical examination, almost all the patients can be diagnosed favourably. Some critical inquiries may help the clinicians in making an accurate diagnosis, one of the important points undoubtedly being the acute or chronic course of pain. New-onset pain is usually related to an acute disease such as septic arthritis, acute rheumatic fever (ARF), viral myositis, osteomyelitis, or trauma. The patient should be asked about the recent history of infection for post-infection arthritis, trauma for orthopedic and mechanical conditions, or raw milk consumption for brucellosis.[7-11] In the presence of single joint involvement and fever, septic arthritis, osteomyelitis, soft tissue infections, and malignancies should be taken into account. In this case, the presence of fever, the history of the previous infection, and trauma should be questioned. While if a patient presents with single joint pain without fever, trauma, mechanical problems, toxic synovitis, and avascular necrosis may be the underlying etiology. Familial Mediterranean fever (FMF) should be considered in patients presenting with fever and recurrent non-erosive arthritis. The presence of migratory arthritis refers to ARF, patients with migratory arthritis should be questioned for a history of upper respiratory tract infection.[7-11]

Table 1
The differential diagnoses of musculoskeletal complaints

Traumatic Fractures	**Neoplasia** (Benign or malign)
Growing pains	Osteoid osteoma
Hypermobility-associated pain	Chondroblastoma
Diffuse idiopathic pain syndromes	Osteoblastoma
Juvenile fibromyalgia	Leukaemia
Complex regional pain syndromes	Lymphoma
Orthopaedic/mechanical	Neuroblastoma
Overuse injury	Ewing's sarcoma
Slipped upper femoral epiphysis	Osteosarcoma
Perthes' disease	Langerhans cell histiocytosis
Osgood Schlatter disease (tibial tuberosity),	**Inflammatory**
Scheuermann's disease	Transient synovitis of the hip
Leg length discrepancy	Juvenile idiopathic arthritis
Club foot	Reactive arthritis
Infectious	Acute rheumatic fever
Septic arthritis	Chronic recurrent multifocal osteomyelitis
Osteomyelitis	Systemic lupus erythematosus (SLE)
Discitis	Juvenile dermatomyositis
Lyme disease	Vasculitis
Brucella	**Other**
	Haemophilia
	Vitamin D deficiency/Rickets

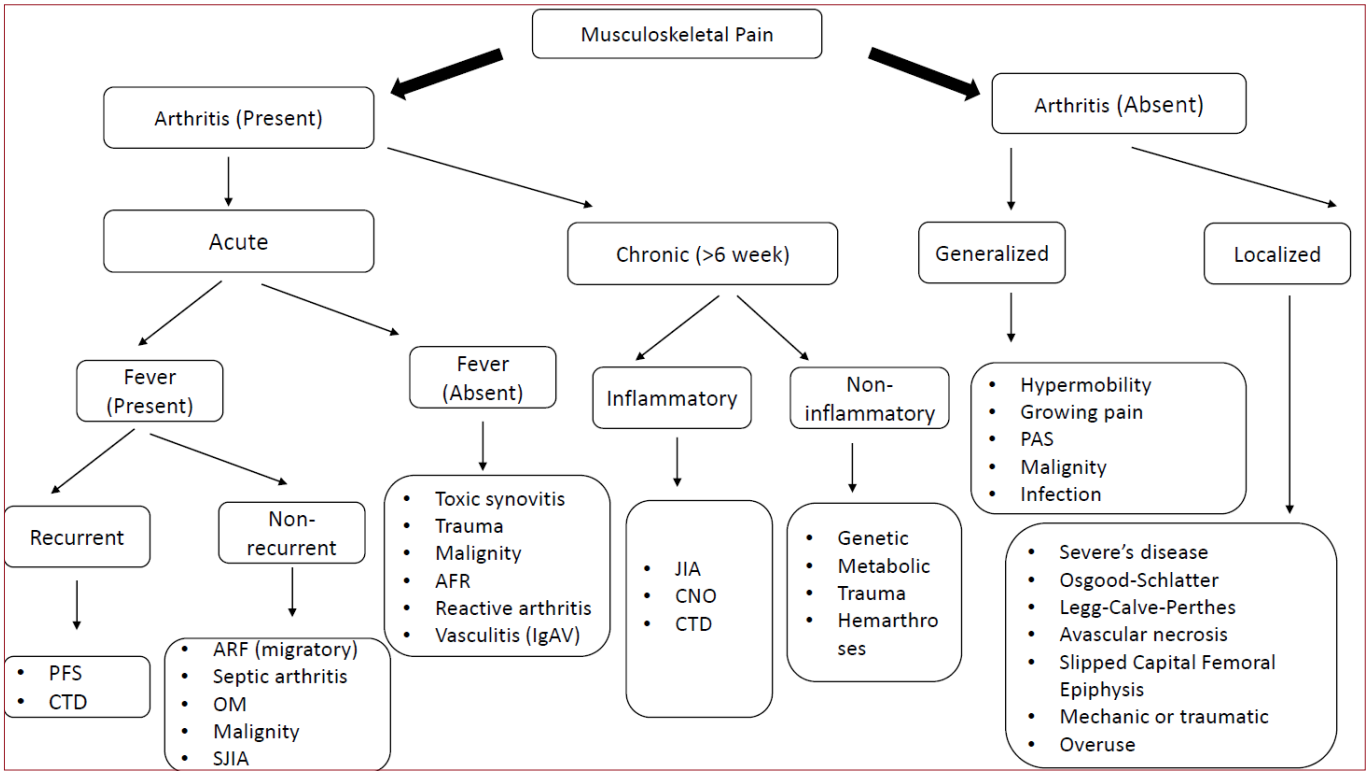

Figure 1. Algorithm for evaluation of children presenting with musculoskeletal complaints

CNO, chronic non-bacterial osteomyelitis;CTD, connective tissue disease; FMF, familial Mediterranean fever; IgAV, Immunoglobulin A vasculitis; JIA, juvenile idiopathic arthritis, PFS; Periodic fever syndrome, ARF; Acute rheumatic fever, OM; osteomyelitis, PAS; Pain Amplification Syndrome, SJIA; systemic juvenile idiopathic arthritis.

When the patients have chronic joint complaints, the character of the pain should be distinguished, that is whether it is of an inflammatory or mechanical type. Mechanical joint pain is more likely to worsen with exercise, while inflammatory joint pain usually occurs in the morning after a long period of immobility and improves throughout the daily exercise. Sports activities and lifestyles should be questioned for sports-related injuries (**Table 2**).[7–11] Children with growing pains present with bilateral awakening leg pain, which is resolved through painkillers or massage. A physical examination of these children is normal and the pain is not accompanied by systemic symptoms such as fever, weight loss, and weakness. If clinicians follow the clues, they can easily distinguish the growing pain. For instance, growing pains are never present at the start of the day after waking and never restrict physical activities. Furthermore, children with growing pain do not limp and their growth development is normal.[7–11]

Table 2
Comparison of mechanical and inflammatory joint problems in children

	Mechanical joint problems	Inflammatory joint problems
Pain worsening with activity	+	-
Pain worsening with rest	-	+
Morning stiffness	-	+
Swelling	-/+	+
Loss of movement	-/+	+
Locking	+	-

Benign conditions present with pain resolving with rest and worsening with activity without obvious joint swelling, constitutional symptoms, and abnormal laboratory findings. Furthermore, extra-articular and systemic symptoms (fever, weight loss, fatigue) usually refer to systemic disease.[7–12] Approximately 20% of children with leukemia present with MSK complaints at the diagnosis.[13,14] Therefore, it is important to follow systemic symptoms such as fever, weight loss, and fatigue. Morning stiffness and unresponsive pain to painkillers often indicate serious conditions.

Juvenile idiopathic arthritis (JIA) is the most common reason for chronic arthritis worldwide. It is a heterogeneous group of disorders presenting with joint inflammation. The presence of morning stiffness for longer than 15 minutes was found to be a strong predictor factor to distinguish JIA among children with MSK complaints.[15]

Len et al.[16] purposed a questionnaire for the early detection of convenient referral to pediatric rheumatology centers. This tool can guide clinicians for early referral of patients with chronic arthropathy to pediatric rheumatology centers. This tool consists of twelve questions and each question scores 1 point in the presence of positive response; if the final score is 5 points or above, the patient has to be referred to a rheumatologist. The affirmational tool questioned the following items:

1. Presence of swollen joints or articulations for the last 7 days.
2. Complaint of pain in the joints, muscles, or bones for the last 7 days without trauma.
3. Swollen joints lasting more than 30 days.
4. Complaint of pain in the joints lasting more than 30 days without trauma.
5. Presence of difficulties in closing the hands, folding the wrists, knees, or ankles.
6. Presence of limping in the last month.
7. Disabilities while playing or running.
8. Waking up with a complaint of pain in the joints.

9. Presence of difficulties in daily activity due to pain in the joints.
10. Presence of deformity in any joint.
11. Presence of fever for more than 30 days without any apparent cause.
12. Presence of rash followed by swelling or pain in the joints.

Physical Examination

Paediatric Gait, Arms, Legs and Spine (pGALS) has been introduced as a simple and quick screening tool for the evaluation of the MSK system in children.[17] This tool is recommended as the initial assessment while evaluating a child with MSK complaints. The accuracy of this tool in Turkish children was tested and its Turkish version was shown as a valid, acceptable, and practical screening test.[18] pGALS is based on methodology as a “copy me” approach. The clinicians show the movements and wait for the patient to imitate them, thus allowing a rapid assessment of the entire MSK system. In the presence of an abnormal finding in pGALS, patients should be examined in more detail.[19]

A comprehensive physical examination should be performed to exclude non-rheumatic conditions. Skin evaluation may provide some clues for accurate diagnosis. For instance, the presence of erythema marginatum or subcutaneous nodules with migratory polyarthritis in a child with a history of throat infection is typical for the diagnosis of ARF. The presence of palpable purpura, especially on the lower extremities, in a patient with arthritis and subcutaneous edema will direct the clinician to the diagnosis of immunoglobulin A (Ig A) vasculitis only by inspection. Furthermore, severe pain in a single joint, redness and increased heat on the affected joint should suggest septic arthritis to physicians. Physical examination including palpation, evaluation of active and passive movements of the joints, and muscle strength examination may reveal the source of pain as either being of joint or muscle origin. Malignancies should be considered in children with insidious onset of symptoms such as weight loss, weakness, fever, widespread extremity pain awakening from sleep at night, and abnormal physical findings such as ecchymosis and petechiae, hepatosplenomegaly, and lymphadenopathy.[7–12]

Although connective tissue diseases are rare in children, children with systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM), juvenile scleroderma, or mixed connective tissue disease may present with arthritis. In patients, especially adolescent girls, presenting with skin findings such as malar rash and photosensitivity concomitant to arthritis and/or myositis the diagnosis of SLE should be kept in mind. In addition, JDM should be considered in children with symmetric proximal muscle weakness and skin findings such as heliotropic rash and Gottron's papules. Therefore, detailed systemic examination, both skins assessmentand MSK examination has great importance in patients with musculoskeletal complaints.

Children with hypermobility usually suffer from chronic MSK pain. The Beighton score is a popular screening technique for hypermobility. It is a nine-point scale including 5 manoeuvres as follows: 1) Passive dorsiflexion and hyperextension of the fifth metacarpophalangeal joint beyond 90°, 2) Passive apposition of the thumb to the flexor aspect of the forearm, 3) Passive hyperextension of the elbow beyond 10°, 4) Passive hyperextension of the knee beyond 10°, 5) Palms of the hands resting flat on the floor.7–12 A positive Beighton score for children is at least 6 out of the 9 points.

By considering the age factor, a detailed joint examination guides the presence of tendinitis, apophysitis, or arthritis. For instance, the calcaneal growth plate is stressed by the Achilles tendon (Sever’s disease) in younger children and older children due to the growth of the immature skeleton apophysitis located to the tibial tubercle or the inferior patellar pool (Osgood-Schlatter disease) ensues.[20]

Laboratory Evaluation

A normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels in a child with chronic joint pain may help to exclude the diagnosis of infections and malignancies. A blood smear should be performed to exclude hematologic malignancies in patients with MSK complaints and systemic features. In the presence of elevated lactate dehydrogenase (LDH) levels, malignancy should be ruled out. Autoantibodies such as ANA and rheumatoid factor (RF) may be positive in healthy children.[20] The positivity rate of ANA and RF in healthy Turkish children was reported to be 4% and 3%, respectively.[21] For this reason, testing ANA or RF is not recommended as a screening test to rule out rheumatologic disease in the primary care setting.[10–12] Furthermore, the antistreptolysin O (ASO) titer should be used to confirm the diagnosis of ARF but it should be kept in mind that ASO titer peaks between three to eight weeks after a streptococcal infection and may remain high for several months.[22] Consequently, the presence of ANA and RF antibodies or elevated ASO does not directly refer to rheumatological diseases and their usage as a screening test causes unnecessary costs and concerns, as well.

Conclusion

In children with MSK complaints, detailed anamnesis, appropriate physical examination and joint examination and the use of correct laboratory tests will provide early access to accurate diagnosis and also reduce the burden of pediatric rheumatology clinics.

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Original Article

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The Importance of Immature Granulocyte and Immature Reticulocyte Fraction for the Severity of Acute Bronchiolitis

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Abstract

The immature granulocyte (IG) and immature reticulocyte fraction (IRF) are new analytical parameters of the complete blood count, that have been studied as biomarkers of several inflammatory conditions. Here, our aim is to determine the effectiveness of IG and IRF percentages for the severity of acute bronchiolitis (AB). A single-center, prospective study was performed in patients who were hospitalized for acute bronchiolitis and healthy children were included as a control group. The demographic characteristics, white blood cell (WBC) count, platelet (PLT) count, eosinophil%, IG%, and IRF% values were analysed. Receiver operating characteristics (ROC) analysis was used to compare the diagnostic accuracies and predictive performances. We enrolled 168 infants in the acute bronchiolitis group and 80 in the control group. The Clinical Severity Score (CSS) showed that 48, 93, and 27 patients had mild, moderate, and severe bronchiolitis, respectively. The WBC, PLT, and IRF value were significantly higher in patients ($p<0.001$). There was no difference between the patients and control group in terms of IG and eosinophil percentage. Only a positive correlation was observed between the clinical severity of the AB and IRF ($p=0.003$).The ROC curve analysis indicated that the IRF% cut-off point for predicting severity AB was >12.4, with a sensitivity of 53% and specificity of 88% (Areas under the curves (AUC):0.701,$p<0.001$). The WBC count, PLT count, and IRF value increased in the AB group. The IRF percentage can be used to predict the clinical severity of AB in children.

Keywords: Acute bronchiolitis, immature granulocyte, immature reticulocyte fraction

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Introduction

Acute bronchiolitis (AB) is one of the most common causes of pediatric emergency room admissions in the first year of life. Viruses are the most common cause of AB, especially respiratory syncytial virus (RSV). It has become one of the most common reasons for hospitalization of children younger than 2 years of age during the winter months. It is characterized by respiratory distress, wheezing, cough, fever, and coryza and is most often associated with RSV infection. The clinical severity of AB ranges from mild cases that can be treated on an outpatient basis to severe cases that require mechanical ventilation in intensive care units. The hospitalization rate varies between 1% and 20% among children less than 24 months of age during seasonal epidemics.[1-4] Most children hospitalized due to AB have an uneventful course; however, approximately 2–6% requires admission to a pediatric intensive care unit (PICU), with 2–3% of hospitalizations requiring invasive mechanical ventilation. The World Health Organization has reported that RSV is the causative pathogen for over 30 million new acute lower respiratory infection episodes in children under 5 years of age and it gives rise to more than 3.4 million hospital admissions and more than150,000 deaths per year.[5-8] Various scoring systems have been developed, but still, there is no biomarker to predict the clinical prognosis of AB in order to reduce the mortality and morbidity of AB in children. Moreover, the biomarker must be fast, inexpensive, simple to measure and effective. Today, automated analyzers measure various complete blood cell (CBC) indices including the white blood cell (WBC) count, platelet (PLT) count, immature reticulocyte fraction (IRF), and immature granulocyte (IG) count. The IRF and IG provide a more precise evaluation of bone marrow activation. Diagnostic accuracy studies performed in the last years suggest that IRF and IG can provide clinically relevant information about inflammatory activity and disease prognosis.[9-12] This study was conducted to determine the effectiveness of immature cells such as IG and IRF for AB severity.

Highlights

- Acute bronchiolitis (AB) is one of the most common causes of pediatric emergency department admissions and hospitalization in the first year of life.
- The clinical severity of acute bronchiolitis ranges from mild cases that can be treated on an outpatient basis to severe cases that need hospitalization to the intensive care units.
- The immature granulocyte (IG) and immature reticulocyte fraction (IRF) are young cells that have been released into the circulation, and are considered indicators of bone marrow recovery and activation.
- A positive correlation was observed between the clinical severity of acute bronchiolitis and IRF.

Material and Method

A single center prospective study of children aged 1–24 months who were hospitalized with AB was performed between Semptember 2018 and May 2019. The study was approved by the local ethics committee. Written informed consent was obtained from all parents/guardians. In accordance with American Academy of Pediatrics guidelines, a diagnosis of AB was based on at least two of the following signs: chest retractions, tachypnea, and the first episode of wheezing or rales on auscultation following a viral upper respiratory tract infection in children aged younger than 24 months.[1] The study included 168 patients with acute bronchiolitis and 80 healthy children. Inclusion criteria were: aged 1–24 months, first wheezing episode, no previous disease history, and no previous medication. Exclusion criteria were: chronic disease, premature birth, birth weight <2500 g, malnutrition, passive smoking, proven immune deficiency, proven or suspected acute bacterial infection, previous treatment with bronchodilators or corticosteroids, or having symptoms for more than 7 days. All patients underwent a routine clinical evaluation in the emergency department by the pediatrician. On admission, the clinical severity score (CSS) for acute bronchiolitis (i.e., a composite clinical score including respiratory rate, retraction, wheezing, and general condition) was used to evaluate patients, as previously described by Wang et al.[13] Patients were divided into three groups as mild, moderate and severe according to the clinical severity score (CSS) of acute bronchiolitis which was previously described by Wang et al.[14] Complete blood count measurements (including white blood cells (WBC), platelets (PLT), eosinophil, IG, IRF) were recorded from the blood samples taken on the first day of hospitalization using an XE-2100 automated hematology analyzer (Sysmex, Kobe, Japan). WBC, PLT, IG, IRF and were obtained from the CBC without receiving any treatment such as steroids. To minimize variations due to sample age, all assays were performed within four hours of collection; the samples were kept at room temperature until the time of analysis. IRF was measured in a dedicated reticulocyte channel of the hematology analyzer by flow cytometry, using a proprietary fluorescent dye containing polymethine and oxazine. The IRF corresponds to the fraction (%) of medium and high fluorescence reticulocytes. Data from each patient recorded in the emergency room included: age, sex, disease history, medication, birth history, whether this was the first attack of bronchiolitis, weight, vital signs (i.e., heart rate, respiratory rate, tympanic temperature, and oxygen saturation when breathing ambient air, which was measured using pulse oximetry and expressed as SpO_2). The control group included 80 healthy children who attended pediatric clinics for routine health checks or vaccinations. They had similar age/sex demographic characteristics to the children with bronchiolitis. Complete blood counts data were obtained from blood samples taken for routine testing of these children at their first visit.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp. Armonk, NY: USA. Released 2013). For the normality analysis of the parametric data, the Shapiro Wilk test was used. Descriptive data were presented with statistical methods mean±standard deviation. Numerical variables were specified as median (min-max). Student's t-test was used to compare the groups with normal distribution. MannWhitney U test was used to compare non-normally distributed groups. Comparison between groups for data that did not show a normal distribution were performed using Kruskal-Wallis Test. The receiver operating characteristic (ROC) curve was used to evaluate the optimal cutoff points of the parameters for which significant differences were found. Sensitivity, specificity, cut-off points, negative predictive value (NPV), positive predictive value (PPV) and the area under the curve (AUC) were calculated for these parameters. The results were analyzed within a 95% confidence interval. A value of p<0.05 and AUC >0.600 was considered statistically significant.

Results

In total, 168 patients were included in this study, 102 (60.70%) of these patients were male and 66 (39.30%) were female. The control group included 80 healthy children, also with a mean age of 7.3±4.28 months, 47 (58.7%) of them were male and 33 (41.3%) were female. The patient and control group did not differ significantly in age or sex (p=0.58 and p=0.56, respectively). Patients had significantly higher WBC, PLT and IRF values compared with the control group (p<0.001) (**Table 1**).

Table 1
Comparison of demographic and laboratory characteristics of the patients and contol group

	Patients group Median (min-max)	Control group Median (min-max)	p
Age (Month)	8 (1-24)	8 (2-24)	0.580
Sex, male (n)(%)	102 (60.70)	47 (58.70)	0.560
IG (%)	0.32 (0.00-4.90)	0.30 (0.02-2.10)	0.216
IRF (%)	13 (3.70-36.60)	9.40 (5.50-16.00)	<0.001
WBC (10⁹/L)	10260 (2040-31000)	6720 (3140-11500)	<0.001
PLT (10⁹/L)	382 (74-746)	288 (101-449)	<0.001
Eozinofil (%)	0.2 (0.00-9.10)	0.20 (0.00-9.10)	0.756

Abbreviations: IG: Immature Granulocyte; IRF: Immature Reticulocyte Fraction; WBC: White Blood Cell; PLT: Platelet.

The patient group included 48 (28.60%), 93 (55.30%), and 27 (16.10%) children classified as having mild, moderate, and severe bronchiolitis, respectively. The median CSS was 6 (range, 2–12). No significant correlation was found between CSS and age, sex, body temperature, oxygen saturation (%), WBC, PLT, IG, and proportion of eosinophils (p>0.05). IRF values differed significantly among the mild, moderate, and severe groups (p<0.001). A positive correlation was observed between the CSS and the IRF (p<0.001). IG value showed a positive correlation with CSS, but it was not statistically significant (p=0.497) (**Table 2**).

Table 2
Comparison of the clinical severity of acute bronchiolitis and laboratory findings

	Mild Median (min-max)	Moderate Median (min-max)	Severe Median (min-max)	p
IG (%)	0.30 (0.00-2.50)	0.35 (0.00-4.10)	0.40 (0.03-4.80)	0.497
IRF (%)	10.50 (4.70-36.60)	14.20 (3.70-35.30)	14.25 (4.40-35.70)	0.003
WBC (10⁹/L)	10.9 (2.81-31.00)	11.570 (4-23.80)	9.79 (4.19-23.80)	0.422
PLT (10⁹/L)	220.50 (88-430)	231.0 (74-631)	218 (88-631)	0.335
Eozinofil (%)	0.5 (0.00-4.70)	0.15 (0.00-9.10)	0.40 (0.00-9.10)	0.280

Abbreviations: IG: Immature Granulocyte; IRF: Immature Reticulocyte Fraction; WBC: White Blood Cell; PLT: Platelet.

ROC curve analyses were used to evaluate the performance of IG and IRF in distinguishing AB patients from controls, and in assessing acute bronchiolitis severity. The AUC for IRF and IG was 0.701, 0.542, respectively. ROC curve analysis suggested that the cut-off for using IRF% to predict severity AB was >12.4, with a sensitivity of 53% and a specificity of 88%. The positive and negative predictive values of the IRF were 91.3% and 45.8%, respectively (p<0.001). The cut-off for using IG% to predict severity acute bronchiolitis was>0.01, with a sensitivity of 2.8% and a specificity of 100% (**Table 3**). The positive and negative predictive values of the IG were 100.0% and 31.5%, respectively (p=0.19) (**Figure 1**).

Table 3
Area under the ROC curves, cut-off values and P-values of immature cells

	Cut-off	Sensitivity %	Specificity %	AUC	95% CI	p
IG (%)	>0.01	2.80	100	0.542	0.39-0.51	0.195
IRF (%)	>12.4	53.10	88.70	0.701	0.64-0.75	<0.001

Abbreviations: IG: Immature Granulocyte; IRF: Immature Reticulocyte Fraction; AUC: Area Under The Receiver Operating.

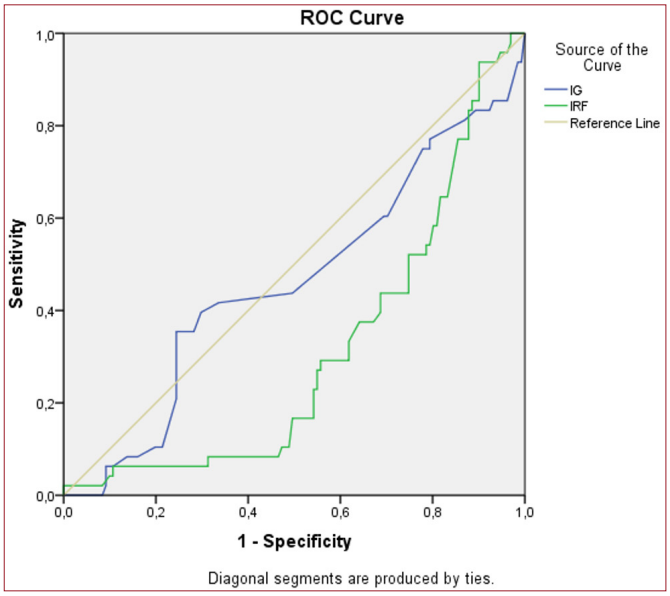

Figure 1. Receiver operating characteristic curve (ROC) analysis of Immature Reticulocyte Fraction (IRF) and Immature Granulocyte (IG).

Discussion

We found that the IRF was greater in patients with AB than in healthy children and was positively correlated with the clinical severity of AB. To the best of our knowledge, this is the first study to investigate IRF and AB severity. The patients with AB and high IRF values should be monitored closely after admission to the emergency department. IRF values higher than 12.4% had a specificity of 88% and a sensitivity of 53% for clinical deterioration of acute bronchiolitis.

The IRF and IG are young cells that have recently been released into the circulation, and are considered indicators of bone marrow recovery and activation. They are important in various clinical conditions such as thrombocytopenia, anemia, inflammation severity, bone marrow regeneration after transplantation of hematopoietic stem cells and after chemotherapy. In recent years, it has been possible to detect the percentage and number of IG and IRF due to technical developments in automated hematological analyzers.[14-17]

IRF is defined as the ratio of young reticulocytes to the total number of reticulocytes. IRF is an examination of bright reticulocyte fraction with a high content of RNA.[18,19] There are different results regarding the normal range of IRF and IG due to the different instruments used in IRF measurement, standardization and calibration problems.[20,21] Gonçalo et al. was accepted the IRF reference median as 4.7% (range: 1.1-11.4%).[15] Use of normal values of the percentage of IG for adults and children, all reported as <1%.[21,22] The reference range of the analyzer in our study was 0-0.9% for IG and 8.4-25.8% for IRF.

IRF value may increase due to increased bone marrow activity in infectious conditions.[12,23] One study found that IRF was significantly higher in patients with sepsis than in healthy individuals (p<0.001) In the same study, higher IRF values were found in patients with severe sepsis compared to patients with sepsis, but no significant difference was found (p=0.53).[10] Park SH et al. found significantly higher IG and IRF values in patients with sepsis compared to patients with non-sepsis (p<0.001, p=0.030 respectively).[24] IRF values higher than 5.6% had a specificity of 56.0% and a sensitivity of 77.6% for diagnosis sepsis (AUC: 0.658). IG values higher than 0.4% had a specificity of 74.5% and a sensitivity of 67.0% for diagnosis sepsis (AUC: 0.812). IG is generated and differentiated in bone marrow, and their presence in peripheral granulocytes circulation indicates greatly increased bone marrow activation due to an infectious condition. The importance of IG is unknown to many clinicians. The IG percentage is defined as the percentage of the total WBC count. Therefore, it is suggested that IG can be considered as a new early diagnosis and prognostic marker in infectious diseases. An elevated IG% implies the enhancement of bone marrow activity to fight against to sources of infections before leukocytosis is occurred.[10,16,25] In addition several recent studies have investigated the role of IG percentage measurement as a potential marker to predict severity of an infection.[25-29] Ansari-Lari et al.[10] found a significantly higher percentage of immature granulocytes in infected than in non-infected patients and designated a percentage of IG of more than three (IG%>3) as a predictor of sepsis, with a specificity of more than 90%. Senthilnayagam et al.[16] found that IG percentage of blood culture positive children patients were significantly higher than in culture negative patients. Pavare et al.[30] found that the cutoff level of IG percentage to predict serious bacterial infections was 0.45 (84% specificity, 66% sensitivity, 90% positive predictive value). Their findings suggest that serious bacterial infections in children is associated with an increase in IG percentage. In our study, similar to the literature IG values were gradually increasing from mild group to severe group, but there was no statistically significant difference (p=0.49). Also, the IG value was higher in the AB group compared to the healthy group, but there was no significant difference (p=0.21). In the literature, we did not find any other study investigating the relationship between acute bronchiolitis and IG other than ours.

This study had certain limitations. Firstly, the findings presented were the experience of a single center and therefore, may not be generalizable to all institutions. Secondly, viral agents of the patients could be determined and compared according to the clinical severity of the disease. The number of patients in need of intensive care, and the hospitalization rate and duration of hospitalization of patients with mild, moderate and severe bronchiolitis were not recorded as our third limiting factor.

Conclusion

Increased levels of IRF, WBC, PLT were observed in the acute bronchiolitis group. Moreover, IRF may be a diagnostic biomarker to assess the clinical severity of acute bronchiolitis. Larger prospective studies are needed to clarify the clinical significance of using IPF values to assess patients with acute bronchiolitis.

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Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Erciyes University Local Ethics Committee (Date: 23.02.2018, Decision No: 2018-91).

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Informed Consent: Informed consent was obtained from the parents of the patients.

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Evaluation of Etiological Causes in Children with Symptomatic Hematuria

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Abstract

Hematuria is an important and common symptom of urinary system pathologies in children, and careful evaluation is required for its definitive diagnosis. This study aimed to determine the demographic and clinical characteristics and etiological causes of patients who applied to our pediatric nephrology clinic with hematuria. In this study, the record of 434 patients who were followed up in our clinic for macroscopic and/or microscopic hematuria were evaluated retrospectively. Demographic data, clinical findings, laboratory and imaging examinations, and final diagnosis of the patients were recorded. Out of 434 patients with hematuria, 239 (55%) were males and 195 (45%) females. Of the patients, 291 (67%) had macroscopic hematuria, and 83 (19.1%) had glomerular hematuria. Non-glomerular causes were found in 80.9%, with a significantly higher rate. Most of the causes of non-glomerular hematuria were urinary tract infection and renal stones. Acute post-streptococcal glomerulonephritis (APSGN) was found to be responsible for the majority of glomerular diseases. This study shows that most pathologies that may cause hematuria can be detected with a detailed history, careful physical examination, and simple laboratory tests.

Keywords: Hematuria, children, etiology, glomerular, non-glomerular

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Introduction

Hematuria is one of the important symptoms encountered in the pediatric age group. It may occur as an initial sign of urinary system disease. It can be macroscopic or microscopic and symptomatic or asymptomatic. The presence of hematuria is indicative of a wide variety of etiologies. Hematuria is defined as centrifuged urine residue containing more than five red blood cells (RBCs) in a 40x magnification field under light microscopy.[1] The prevalence of microscopic hematuria varies between 0.15-2%. with an estimated incidence of 1.3 per 1000 children.[2,3]

Hematuria can originate from the upper or lower urinary tract. The upper urinary tract sources are the glomerulus, tubular system, or interstitium. The pelvicalyceal system, ureter, bladder, and urethra are sources of hematuria in the lower urinary tract.[4,5] The diagnosis of hematuria is made with a detailed history, systemic physical examination, and laboratory tests. In urine microscopy, the presence of dysmorphic RBC with distorted contours is typical for almost glomerular hematuria.[6]

Highlights

- Hematuria is one of the important symptoms in the pediatric age group.
- It can be macroscopic or microscopic and symptomatic or asymptomatic.
- The presence of irregular, dysmorphic RBC with distorted contours in urine microscopy indicates the outflow of erythrocytes from the glomerular capillaries into the urinary cavity and is almost pathognomonic for glomerular hematuria.

Under physiological conditions, endothelin windows (50-100 nm) are thought to act as self-contained molecular-sized sieves to keep RBCs (6.2-8.2 µm) away from the glomerular basement membrane (GBM). How RBCs that are 100 times larger than the pores of the glomerular endothelium cross the GBM remains unclear. The release of inflammatory or chemotactic signals that promote RBC passage through a damaged glomerular filtration barrier (GFB) layer has been implicated, but specific mechanisms have yet to be clarified.[7] The change in the morphology of erythrocytes is due to mechanical damage as they pass through the glomerular basement membrane and osmotic damage as they pass through the nephron. Therefore, glomerular hematuria indicates dysfunction and damage to the glomerular basement membrane.[8]

Knowing the causes of hematuria and their frequency facilitates the approach of clinicians. This study aimed to determine the demographic, clinical characteristics, and etiological causes of patients who applied to our pediatric nephrology clinic between 2016 and 2021 with symptomatic hematuria.

Material and Method

The records of 434 patients who were followed up in Fırat University Pediatric Nephrology Clinic between 01 July 2016 and 30 June 2021 due to macroscopic and/or microscopic hematuria were evaluated retrospectively. Patients with red urine but no erythrocyte detected in urine microscopy were not included. Demographic data, onset and duration of signs and symptoms, clinical findings, family history of chronic kidney disease, and laboratory results were recorded. The study was approved by the ethics committee of Fırat University on the 10.02.2022 date and with an issue protocol number of 2022-02-17. Macroscopic hematuria may be bright red or brown-colored with or without visible clots. Microscopic hematuria is defined as a significant number of red blood cells (>5/HPF) in the urine without color change. After the urine of the patients was centrifuged at 2000 rpm (revolutions per minute) for 10 minutes for microscopic examination, the presence of five or more erythrocytes at 40x magnification was defined as hematuria.[1] Glomerular hematuria was differentiated from non-glomerular hematuria by the presence of dysmorphic RBCs, erythrocyte cast, and proteinuria.[9]

In addition, urinalysis, complete blood count, coagulation parameters, urea, creatinine, total protein, albumin, serum electrolytes, and urinary ultrasonography information was recorded. Anti-streptolysin O titers, throat culture, urine culture, antinuclear antibodies, anti dsDNA antibodies, peripheral and cytoplasmic nuclear antibodies were measured in selected patients for diagnosis. The patients who underwent computed tomography and magnetic resonance imaging within the indications were scanned. Ophthalmologic and audiometric examinations were reviewed in patients with a family history of chronic kidney disease, Alport's disease, hematuria, deafness, and/or ophthalmologic problems. Renal biopsy was performed in selected cases such as unidentified and recurrent macroscopic hematuria, microscopic hematuria with proteinuria lasting longer than six months, family history of hematuria, or end-stage renal disease suggestive of glomerular disease.[1] The patients' data were recorded, and their final diagnoses were evaluated.

Statistical analysis was performed with the IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp.). Data were expressed as the median and interquartile range for quantitative nonparametric measures as the mean and standard deviation (SD) for parametric data.

Results

Out of 434 patients with macroscopic or microscopic hematuria, 239 (55%) were male, and 195 (45%) were female, with a male/female ratio of 1.22 (**Table 1**). The mean age of the patients was seven years and six months (between 1 month and 17 years). At admission, red urine was the first complaint, with a rate of 46%. Followed by abdominal pain with 12.4%, dysuria with 6.2%, and fever with 5.2%. While the complaint of swelling in the body was 5.2%, the rash rate was 3.2%. Other complaints (21%) included decreased urine, inability to urinate, decreased feeding, restlessness, vomiting, sore throat, cough, constipation, joint pain, diarrhea, urinary incontinence, and nose bleeding. While 292 (67%) patients had macroscopic hematuria, 143 (33%) patients had microscopic hematuria. In light microscopy, 80.9% of the erythrocytes were morphic, and non-glomerular hematuria was detected. In

comparison, 19.1% of them were found to have glomerular hematuria with the presence of dysmorphic erythrocytes and erythrocyte casts (**Table 2**).

Table 1
Distribution of hematuria cases according to age groups and gender

Age	Female n	Male n	Total n	%
0-5	68	83	151	34.7
6-11	80	97	177	40.8
12-18	47	59	106	24.5
Total	195	239	434	100

Table 2
Classification of patients with symptomatic hematuria

Etiology	n (434)	%
Glomerular diseases	83	19.1
Non-glomerular diseases	351	80.9

Out of 83 (19.1%) patients with glomerular hematuria, 36.3% were acute post-streptococcal glomerulonephritis, the first among glomerular causes. This was followed by nephrotic syndrome with 24% and Henoch Schönlein Purpura (HSP) nephritis with 16.8%. Other causes of glomerular hematuria were Alport's disease, IgA nephropathy, thin basement membrane disease, and Wegener's granulomatosis (**Table 3**).

Table 3
Diagnosis of patients with glomerular hematuria

Glomerular diseases	n (83)	%
APSGN	30	36.3
Nephrotic syndrome	20	24.1
HSP	14	16.8
Alport's Disease	4	4.8
Ig A nephropathy	3	3.6
FMF	6	7.2
HUS	5	6.0
Wegener's granulomatosis	1	0.2

APSGN: Acute poststreptococcal glomerulonephritis, HSP: Henoch Schonlein Purpura, FMF: familial mediterranean fever, HUS: hemolytic uremic syndrome

Urinary tract infection was the most common cause in 42% of 351 patients with non-glomerular hematuria. This was followed by nephrolithiasis, upper respiratory tract infection, crystalluria, obstructive uropathy, nutcracker syndrome, and idiopathic causes. More rarely, other causes such as thrombocytopenia, menstruation, dehydration, trauma, exercise, hemolytic anemia, sexual abuse, left accessory renal vein, celiac disease, and renal cyst were recorded (**Table 4**).

Table 4
Diagnosis of patients with non-glomerular hematuria

Non-glomerular Diseases	n (351)	%
Urinary tract infection	149	42
Renal stone	60	17
Upper respiratory tract infection	27	7.6
Crystalluria	12	3.5
Obstructive uropathy	10	2.8
Nutcracker Syndrome	8	2.2
Other causes	31	9.1
Idiopathic causes	54	15.8

Other causes: Heavy exercise, trauma, thrombocytopenia, hemolytic anemia menstruation, sexual abuse, renal cyst, nephrocalcinosis, dehydration, celiac disease.

Computed tomography was performed in 31 (7.4%) patients; magnetic resonance imaging was performed in 6 (1.3%) patients. Among the patients with glomerular hematuria, 29 patients (6.6% of all patients) underwent kidney biopsy within the indications. Considering the distribution of patients who underwent kidney biopsy by years, there was no significant difference, and approximately 50% were performed within the last two years. Of 29 patients who underwent kidney biopsy, 9 had membranoproliferative glomerulonephritis (MPGN), 7 had HSP nephritis, 6 had APSGN, 3 had IgA nephropathy, 2 had focal segmental glomerulosclerosis (FSGS), one had Alport's disease, and one had thin membrane disease.

Discussion

Hematuria is a worrying condition for both the family and the child. It can be asymptomatic and a symptom of severe kidney disease. Macroscopic hematuria is a significant health problem that causes families to seek immediate medical attention. Microscopic hematuria is often detected incidentally or during school or community screening programs and is more common than macroscopic hematuria.[10-12] As our study included patients presenting with symptoms, macroscopic hematuria was found more frequently than microscopic hematuria (67% versus 33%). Another study was conducted by Youn T. et al.[13] was performed on the medical records of 1001 children and adolescent patients with gross hematuria. Glomerular gross hematuria was found in 24 patients, and the cause was most commonly Ig A nephropathy. Alport's syndrome non-glomerular gross hematuria was found in 56 patients, and the most common etiologies were hypercalciuria, urethrorrhagia, and hemorrhagic cystitis. No etiology was found in 26 patients. Arı et al.[14] conducted a retrospective study with 370 pediatric patients, whose mean age was 7 ± 3.5 years, 52% boys and 48% girls and similar to our research, they found a higher rate of macroscopic hematuria than microscopic hematuria; also non-glomerular causes were detected more frequently with a rate of 72.4%. In our study, non-glomerular causes were seen at a rate of 80.9%, and they were more common than glomerular causes. By the literature, the most common non-glomerular cause was urinary tract infection, followed by renal stone.

It is known that a systematic approach is required after a detailed history and careful physical examination to determine the cause in a pediatric patient with hematuria. Symptoms determined by a thorough history will be helpful for the clinician to reach the diagnosis from signs and prevent unnecessary laboratory tests. It would be appropriate to perform step-by-step tests to confirm the diagnosis according to the findings detected in the patient after the initial evaluation. (**Figure 1**). Renal Doppler ultrasonography is a recommended method for imaging, especially in cases of unexplained hematuria with or without abdominal pain. According to reports, Nutcracker syndrome is one of the leading causes in children with isolated hematuria and proteinuria without urinary tract infection. Renal Doppler ultrasonography is considered the first screening tool to detect nutcracker syndrome.[15,16] Shin et al.[16] detected nutcracker syndrome in 60 of 149 patients with isolated hematuria. In another study evaluating the

etiology of hematuria in children, it was reported that NS was seen in 0.7% of the cases.[14] In our study, nutcracker syndrome was found in 2.2% of patients with hematuria.

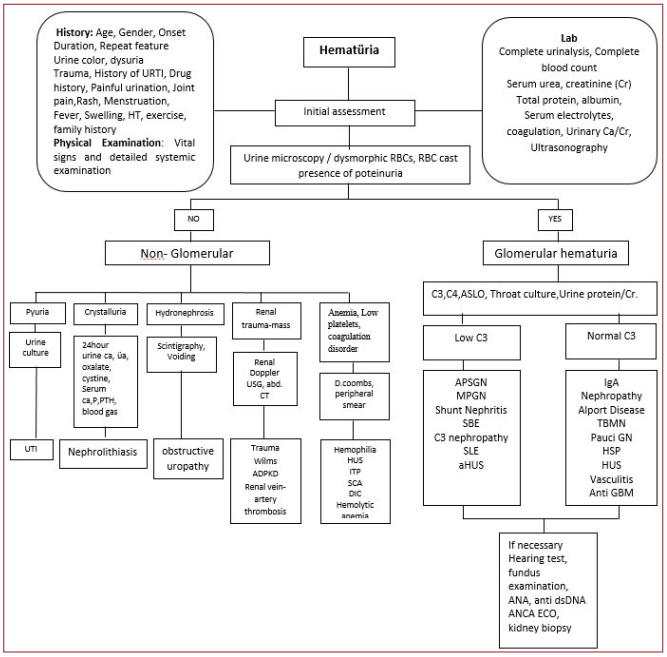

Figure 1. Diagnostic algorithm for hermaturia

URTI: Upper respiratory tract infection, UTI: Urinary tract infection Ca: calcium, P: phosphate, APSGN: Acute poststreptococcal glomerulonephritis, HSP: Henoch Schonlein Purpura, , HUS: Hemolytic uremic syndrome , SBE: Subacute bacterial endocarditis, TBMN: Thin glomerular basement membrane disease, SCA: sickle cell anemia C3: complement factor 3, ASLO: antistreptolysin O, CBC: complete blood, C4: Complement factor 4, ANA: Antinuclear antibody, anti dsDNA: Anti-doublestranded DNA antibody, ANCA: Antineutrophil cytoplasmic, ECO: Echocardiography

A 10-year retrospective review of 342 children who presented with gross hematuria to a pediatric urologic center in the United States reported that no cause could be determined in 35% of the patients.[17] However, in our study, 15% of the patients had no cause that could be determined.

Kidney biopsy is indicated in selected patients with hematuria. The presence of a family history of hematuria or nephritis, accompanying proteinuria, prolonged hypocomplementemia and hypertension, persistent microscopic hematuria, or recurrent macroscopic hematuria are common indications for renal biopsy.[18,19] In this study, 29 (6.6%) of the patients underwent renal biopsy, and the most common histopathological finding was MPGN. Although IgA nephropathy was the most common finding in Lee et al.[20] we think that the rarity of IgA nephropathy in our study is that it only included cases with symptoms.

Conclusion

In this study, we found that the etiology of the majority of patients who applied to our tertiary clinic in the eastern region of our country (Turkey) with hematuria could be clarified as a result of detailed history, detailed physical examination, and basic laboratory tests that could be performed in a secondary health institution. Further imaging studies and renal biopsy are indicated in selected cases.

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

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Fırat University Ethics Committee (Date: 10.02.2022, Decision No: 2022-02-17).

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Informed Consent: Informed consent was obtained from the parents of the patients.

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Can Point Shear Wave Elastography be Used as an Indicator of Metabolic Complications in Overweight Children and Adolescents? Evaluation of Subcutaneous Adipose Tissue

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Abstract

This study aims to search the association of obesity, metabolic parameters, and abdominal subcutaneous white adipose tissue (scWAT) stiffness in children and adolescents using ultrasound point shear wave elastography (p-SWE). One hundred and forty overweight or obese children referred to as overweight were included in the study group. Thirty-two lean children, referred to as leans, were included in the control group. In all individuals, scWAT shear wave speed (SWS) was measured with p-SWE. ScWAT stiffness was compared between the two groups. The association of anthropometric, metabolic factors and scWAT stiffness is determined. Weight, body mass index, body mass index-standard deviation score, systolic blood pressure, diastolic blood pressure, alanine aminotransferase, fasting insulin were significantly higher in the overweight group ($p<0.05$). ScWAT SWS was significantly different between the groups ($p=0.006$) The median value of scWAT SWS was 1,5 m/s (range; 0.9-3.8), 1.23 m/s (range; 0.7-3.1) for leans and overweight, respectively. In leans, no significant difference was found between boys and girls for scWAT SWS ($p=0.094$). In overweight, a significant difference was found for scWAT SWS between boys and girls ($p=0.022$). The scWAT stiffness is lower in overweight than leans. Gender has a pivotal role in scWAT stiffness. If supported with future long-time follow-up studies, p-SWE may be compatible with assessing subcutaneous adipose tissue changes related to obesity and metabolic complications in childhood and adolescence.

Keywords: Obesity, adipose tissue fibrosis, childhood, shear wave elastography

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Introduction

Childhood obesity is a significant health problem in industrialized countries.[1] The prevalence rates for obesity and overweight are reported as 9.8% and 23.2%, respectively, in Turkish children.[2]

In obesity, adipose tissue mass increases depending on adipose cells' expansion and new adipose cells' genesis.[3] An increase in adipose tissue mass is associated with adipose tissue inflammation and eventually fibrosis, which plays a leading role in metabolic dysfunction. Like other fibrotic diseases, increased production and accumulation of extracellular matrix (ECM) proteins are in charge of adipose tissue fibrosis.[4,5] ECM can be reshaped to adapt to normal fluctuations in adipocyte size,in healthy adipose tissue. However, in fibrotic adipose tissue, ECM cannot be dynamically remodeled to accommodate excess lipid storage.[6] This inability of adipocytes to enlarge may beat a path for ectopic deposition of fat into the liver and other organs, thus promoting metabolic complications.[7]

Highlights

- Subcutaneous white adipose tissue (sc WAT) stiffness was significantly lower in overweight than lean children
- Gender has a pivotal role in scWAT stiffness.
- Future long-time follow-up studies are needed to reveal the relationship of subcutaneous adipose tissue changes and obesity-metabolic complications in childhood and adolescence.

Assessment of subcutaneous white adipose tissue (sc WAT) fibrosis may provide valuable clues to determine the metabolic complications in obesity. ScWAT morphology and fibrosis can be determined through surgical biopsies.[8] Unfortunately, this procedure can only be used for experimental purposes because it is challenging to apply and repeat. Therefore, noninvasive techniques are needed. Currently, there are no noninvasive techniques in practical use that simply characterize scWAT fibrosis. Adipose cell hypertrophy, inflammation, and fibrosis may affect tissue hardness as observed in the liver. Recently, ultrasound elastography techniques have emerged to detect liver and other parenchymal tissue hardness.[9-15] Based on these circumstances, an ultrasound elastography technique called shear wave elastography (SWE) is used to search for scWAT fibrosis in the current study.

With the growing obesity epidemic, screening adipose tissue fibrosis can give usefull information about patient outcomes and therapeutic options. The present study aimed to search the association of obesity, metabolic parameters, and abdominal scWAT stiffness in children and adolescents using ultrasound p-SWE.

Material and Method

Study Population

This study was carried through the Department of Pediatric Radiology and the Department of Pediatric Endocrinology. One hundred seventy-two cases who were 8-18 years old were included in the study. The study and control group were defined according to the body mass index-standard deviation score (BMI-SDS) of individuals. One hundred and forty of them were overweight and obese children which were referred as overweight and included in the study group. Thirty- two of them were leans and included in the control group. Children under eight years old were excluded because of the short duration of obesity to develop metabolic complications.

Ethical Aspects

The local ethics committee approved the study. Written consent was obtained from patients and/or their parents.

Clinical and Laboratory Findings

Body mass index (BMI) is calculated by dividing weight by the square of the height. BMI-SDS was calculated according to growth charts using sex and age. [16] Individuals were grouped as leans (BMI-SDS < +1SD), overweight (+1SD < BMI-SDS ≤ +2SD), and obese (BMI-SDS > +2SD).[17] In this study, all of those with BMI-SDS > +1 SD (overweight and obese) were categorized as overweight.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose, fasting insulin, homeostatic model assessment-insulin resistance (HOMA-IR), triglycerides concentrations, high-density lipoprotein (HDL) cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT) were recorded for all participants. The following formula was used for calculating HOMA-IR: fasting plasma glucose (mg/dL) × fasting plasma insulin (IU/mL)/405.[18] These parameters were obtained within a week before or after the elastography measurements. The radiologist was blinded to the metabolic parameters of individuals.

Conventional Ultrasound Evaluation and p-SWE Measurements

All ultrasound examinations were performed by a single radiologist with 18 years of experience in abdominal ultrasonography and two years in SWE. Acuson S3000, Helix Evolution Ultrasound System (Siemens) with a 9L4 linear transducer is used for the examinations.

Shear wave elastography (SWE) is one of the ultrasound elastography techniques, using shear wave speed (SWS) to determine tissue hardness. During the real-time B mode ultrasound imaging, localized transient displacements in the tissue forming the shear waves are generated by applying a short duration acoustic push pulse The velocity of shear waves is recorded. In point shear-wave elastography (p-SWE), a region of interest (ROI) box is put on the interested body areas for elastography measurements. The measurement is expressed either in m/s or kPa, which are changeable during the examination. The square root of tissue elasticity is proportional to SWS which directly relates to tissue hardness.[19-21] This means that the harder the tissue, the faster the shear wave spreads. Extracellular matrix components, primarily fibrotic deposits (i.e., collagen), are known as the main factors affecting tissue hardness.[22]

Grayscale ultrasonography and elastography measurements were performed in the supine position. The transducer was put on the right side of the patient's abdomen, approximately 5 cm laterally from the umbilicus, where abdominal scWAT is at its maximum thickness. Firstly, scWAT thickness was measured and recorded in millimeters. Then, elastography measurements were performed and recorded in m/s. P-SWE was used for elastography measurements with an ROI of 1.0 x 0.5 cm (**Figure 1**). To average the effect of scWAT heterogeneity, SWE measurements were performed on multiple sites neighboring each other. Measurements were obtained during superficial breathing to avoid invalid measurements. The mean of 10 valid measurements for scWAT SWS was recorded. The screen displayed ''xxx,'' when the measurements were invalid. So, such measurements were repeated. The exam duration time was approximately five minutes. The intraobserver agreement expressed as interclass correlation coefficient was 0.96 for p-SWE measurements (95 % CI, 0.95-0.97; p <0.001), demonstrating that the p-SWE measurements had perfect agreement reproducibility.

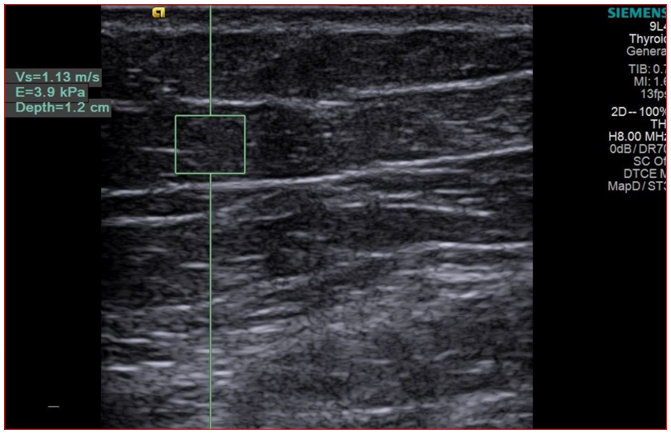

Figure 1. A 10-year-old overweight boy. P-SWE measurement of subcutaneous adipose tissue with an ROI

Statistical Analysis

Analyses were performed with SPSS IBM Statistics Version 22.0. The Shapiro-Wilk test was used to confirm the normality of distribution for quantitative data. Two independent groups were compared by t-test or Mann-Whitney U for normally distributed data and non-normally distributed data, respectively. Test values were expressed as the mean ± SD. Pearson correlation was used for normally distributed data, and Spearman correlation was used for non-normally distributed data. Correlation analyses were performed for lean boys, lean girls, overweight boys, and overweight girls separately. The interclass correlation coefficient was used for reliability measurements. Differences were regarded as significant at p<0,05.

Results

The age of overweight children enrolled in this study was between 8 and 18 (mean; 12.93 ± 2.52). Fifty-nine of them were boys, and 81 of them were girls. The age of lean children was between 8 and 17 (mean; 13.06 ± 2.58). Eight of them were boys, and 24 of them were girls. The leans and overweight subjects were compared in terms of age, gender, anthropometric, metabolic parameters, scWAT thickness, and scWAT SWS. No significant differences were found between the two groups for age, gender, height, fasting glucose, triglycerides level, AST, and HOMA-IR. Weight, BMI, BMI-SDS, SBP, DBP, fasting insulin, ALT, scWAT thickness were significantly different between the groups. Also, scWAT SWS was significantly different between the groups (p=0.006). The median value of scWAT SWS was 1.5 m/s (range; 0.9-3.8) and 1.23 m/s (range; 0.7-3.1) for leans and overweight, respectively (**Table 1**).

Table 1
Comparison of demographic, anthropometric, metabolic, and laboratory parameters of leans and overweight

	Leans Median (range)	Overweight Median (range)	p
Gender			0.072
Girls	24	81	
Boys	8	59	
Age	13.2 (8-17.4)	3.4 (8.1-18)	0.830
Weight (kg)	46.5 (22.1-83)	73.2 (29.5- 127)	<0.001
Height (cm)	156 (121.5-183.5)	156,5 (117.3-188)	0.58
BMI (kg/m2)	18.9 (14.1-26.2)	28 (18.7-42.8)	<0.001
BMI-SDS	-0.55 (-2.48-1)	2.5 (1.1-4.2)	<0.001
SBP (mmHg)	100 (90-110)	110 (90-140)	0.013
DBP (mmHg)	60 (50-80)	70 (50-90)	0.010
Triglycerides (mg/dl)	98 (28-149)	105 (41-391)	0.062
HDL cholesterol (mg/dl)	52.0 (39-78)	44.0 (28.4-86)	0.001
Fasting glucose (mg/dl)	84.5 (61-95)	87.0 (65-106)	0.388
Fasting insulin (µIU/ml)	9.1 (4.4-15.8)	15.5 (1.4-76.4)	0.012
HOMA-IR	1.85 (0.91-12.4)	3.6 (0.3-17)	0.201
AST (IU/L)	23.5 (17-40)	22.0 (10-84)	0.98
ALT (IU/L)	14 (5-62)	19 (6-158)	<0.001
ScWAT thickness (mm)	13.7 (5-33)	38.0 (9.5-75.0)	<0.001
ScWAT SWS (m/s)	1.5 (0.9-3.8)	1.23 (0.7-3.1)	0.006

BMI, body mass index; BMI-SDS, body mass index-standard deviation score; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HDL cholesterol, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HOMA-IR, homeostatic model assessment-insulin resistance; ScWAT, subcutaneous white adipose tissue; SWS, Shear wave speed

ScWAT thickness and scWAT SWS were compared according to gender in leans and overweight. In leans, no significant difference was found between boys and girls for scWAT thickness and SWS. In overweight, no significant difference was found for scWAT thickness between boys and girls. However, a significant difference was found for scWAT SWS between boys and girls in overweight (p=0.022). The median value of SWS was 1,36 m/s (range; 0.71-3.07), 1.12 m/s (range; 0.70-3.04) for overweight boys and overweight girls respectively (**Table 2**, **Figure 2**).

Table 2
Comparison of scWAT thickness and SWS in leans and overweight according to gender

	Leans			Overweight		
	Boys	Girls	p	Boys	Girls	p
ScWAT thickness (mm) Median (range)	11.7 (5-22.7)	14.9 (4.9-33)	0.254	39.0 (9.5-75)	38.0 (18.30-75)	0.47
ScWAT SWS (m/s) Median (range)	1.66 (1.25-3.80)	1.37 (0.86-2.22)	0.094	1.36 (0.71-3.07)	1.12 (0.70-3.04)	0.022

ScWAT, subcutaneous white adipose tissue; SWS, Shear wave speed

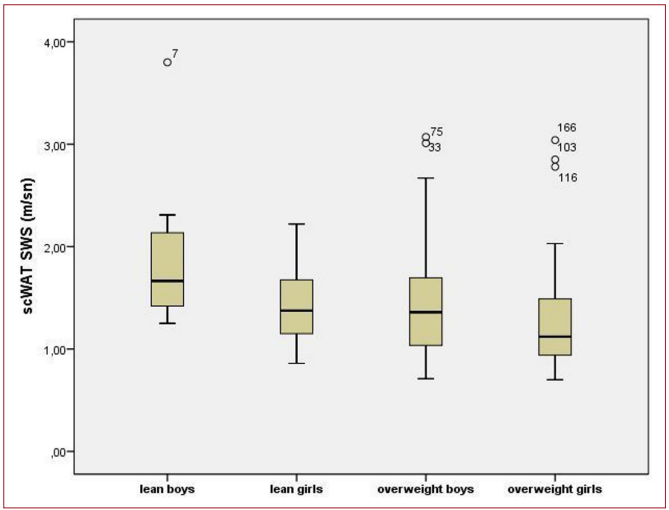

Figure 2. Box-plot showing scWAT SWS of lean boys, lean girls, overweight boys, overweight girls

Correlation analysis was performed between SWS, demographic and laboratory parameters for leans and overweight according to gender. For lean boys, SWS showed no correlation with anthropometric, metabolic, laboratory parameters, and scWAT thickness. For lean girls, SWS showed a relatively strong negative correlation with BMI (r=-0.678 p<0.001), BMI-SDS (r=-0.499 p=0.013), SBP (r=-0.638 p=0.035), DBP (r= -0.695 p=0.018), a relatively strong positive correlation with HDL cholesterol (r=0.616 p=0.033) and a strong negative correlation with scWAT thickness (r= -0.815 p<0.001). For overweight boys, SWS showed a weak positive correlation with ALT and a moderate negative correlation with scWAT thickness. For overweight girls, SWS showed a weak negative correlation with fasting glucose and scWAT thickness (**Table 3**).

Table 3.
The results of correlation analysis between SWS and anthropometric, metabolic, laboratory parameters in overweight boys and girls

	SWS for overweight boys (m/s)	SWS for overweight girls (m/s)
Fasting glucose (mg/dl)		-0.231 0.039
ALT (IU/L)	0.279 0.037	
scWAT thickness (mm)	-0.364 0.005	-0.288 0.009

The first line is r value, the second line is p value for all parameters. ALT, alanine aminotransferase; ScWAT: subcutaneous white adipose tissue; SWS, Shear wave speed

Discussion

Adipose tissue fibrosis has a critical and complicated role in obesity and metabolic dysfunction. The development of adipose tissue fibrosis is associated with some cell types, cellular pathways, or environmental factors, but the inclusionary cause is obesity.[6,23-25] Adipocytes, adipocyte progenitors, myofibroblasts, and fibroblasts are in charge of the production of ECM. Another prominent participant in the development of fibrosis is hypoxia. Hypoxia occurs when adipocytes reach the diffusion limit of oxygen due to lipid accumulation—long-term hypoxia agglomerates macrophages to the area. Also, mast cells contribute to the development of fibrosis by promoting collagen production. It was shown that obese subjects had more pericellular fibrosis accompanied by accumulation of macrophage and mast cells compared with normal-weight subjects. Despite all this information, the association between obesity and adipose tissue fibrosis is complex and is not entirely understood. The prevalence of adipose tissue fibrosis increases with severe obesity, but not all obese patients develop tissue fibrosis.[6]

Depending on the studies,[5,26-29] reporting a close association between obesity and adipose tissue fibrosis and the effects of fibrosis on tissue stiffness,[9-13] it may be anticipated that being overweight may potentially increase scWAT stiffness, in the current study. However, the results showed contradistinction with this expectancy. ScWAT stiffness was significantly lower in overweight than leans. Despite the greater adipose tissue thickness, lower SWS in overweight may be explained by the 'adipose tissue expandability' concept,[30] which states that adipocytes' capacity to expand for lipid storage differs in individuals. It also states that lipid storage capacity is a more determinative factor of obesity-associated metabolic complications than the amount of adipose tissue fibrosis. Patients with higher storage capacity compared with others may have fewer metabolic complications. Short-term exposure to obesity or its complications, might be an explanatory factor for the lower tissue stiffness in overweight children which potentially may affect the development or maintenance of fibrosis in adipose tissue. Charmaine S.T. et al.[31] determined the immunohistochemistry of subcutaneous adipose cells and ECM markers in children. They reported that overweight children had significantly less total collagen staining compared to normal-weight children. Also, they said that the percentage of total collagen was inversely associated with the BMI Z score. In their study, Walker et al.[32] observed a trend in decreasing collagen ratio in obese children compared with leans. These two studies' findings are supporting the lower adipose tissue stiffness in overweight children in the current study.

When SWS was evaluated according to gender, there was no difference in the leans. Conversely, it was interesting to see that girls' SWS values were significantly lower than boys in overweight. This may be explained by the fact that girls gain more fat mass during puberty and less muscle than boys.[33] The 'adipose tissue expandability concept' may also have a role in this situation, with increased lipid capacity of adipocytes causing less tissue stiffness.

After this stage of the study, the correlation analysis between scWAT SWS and the other parameters was performed separately according to gender. There were negative relationships between SWS and BMI, BMI-SDS, SBP, DBP, scWAT thickness, and a positive relationship between SWS and HDL cholesterol in lean girls (**Table 3**). In overweight girls, all these relationships disappeared, and weak negative correlations were seen between SWS and fasting glucose, scWAT thickness. In overweight boys, a weak positive correlation was seen between SWS and ALT. There are few studies[34,35] using elastography to assess scWAT fibrosis in adults and children. Sasso et al.[34] in their study, reported a negative correlation between SWS and total body fat

mass, cholesterol and a positive correlation between total body lean mass, fasting glycemia, fasting insulin, and HOMA-IR. Abdennour et al.[35] in a study in morbidly obese adults, assessed scWAT stiffness and compared the values with immunohistochemistry (IHC) evaluated scWAT fibrosis. They found that scWAT stiffness was positively associated with scWAT IHC fibrosis. They also reported that SWS correlated positively with fasting glycemia, insulin, HbA1c, fat-free mass, and negatively with body fat and HDL cholesterol. In the current study, BMI and BMI-SDS were used to evaluate body fat instead of measuring total body fat. BMI is reported as having a high discriminatory power to identify body fat.[36] The negative correlations between SWS and weight, BMI, BMI-SDS in lean girls, in the current study were similar to their results. It was intriguing not to see a relationship between SWS and anthropometric factors in overweight while seeing in lean girls. Although the reason for this result is unknown, further long-time follow-up studies are needed to elucidate the relation of scWAT SWS and anthropometric, metabolic parameters as the duration of obesity increases.

This study has significant limitations. One of them is the lack of scWAT biopsy for histological confirmation. However, it was impossible to achieve histologic samples as there was no indication. The second limitation is the short duration of obesity in children and adolescents to see the effects of anthropometric and metabolic parameters on scWAT properties. The lack of knowledge of fat mass may be another limitation. A more comprehensive examination of body composition (waist circumference, BMI, fat-free mass, fat mass) in future studies may give more apparent findings.

This is the first study searching the association of anthropometric, metabolic parameters, and scWAT stiffness in children using p-SWE, to our knowledge.

Conclusion

Stiffness of scWAT was found lower in overweight than in leans, and gender had a pivotal role in scWAT stiffness. If supported with future long-time follow-up studies, p-SWE can be compatible with assessing subcutaneous adipose tissue changes related to obesity and metabolic complications in childhood and adolescence.

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

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Erciyes University Ethics Committee (Date: 20.01.2021, Decision No: 2021/63)

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The Effect of Vitamin D Administration on Androgen Levels in Addition to Metformin Treatment in Adolescent Girls with Hyperandrogenism

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Abstract

This retrospective study was planned to examine the relationship between glucose metabolism, androgen and lipid profiles after vitamin D and metformin treatments in adolescent girls with hyperandrogenism. Forty-five adolescent female patients diagnosed with hyperandrogenism were divided into three groups. The first group of patients was given metformin (M), the second group was given metformin and vitamin D drops (MdD), and the third group were those who received oral metformin and vitamin D ampoules (MsD). Biochemical and hormonal parameters at the end of 8 weeks were compared statistically. The vitamin D level was higher in the metformin-vitamin D stoss treated group than metformin-vitamin D drops. There was a positive correlation between vitamin D and SHBG in the metformin group ($r = 0.65$, $p<0.01$). A significant correlation was observed between triglyceride and insulin in both groups given vitamin D, and there was a decrease in these two values ($p<0.05$). There was a positive correlation between total testosterone and Alanine transaminase (ALT) in the MsD group ($p<0.05$). Additionally, a positive correlation was observed between SHBG and HDL-cholesterol in three groups. There was a significant correlation between androgen and lipid parameters in the 8-week metformin and vitamin D treated groups. Long-term studies using high-dose vitamin D are needed to support our results.

Keywords: Hyperandrogenism, adolescent, vitamin D, metformin, testosterone

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Introduction

Hyperandrogenism causes chronic anovulation in girls and causes many clinical findings such as polycystic ovary syndrome (PCOS), obesity, systemic arterial hypertension, dyslipidemia, and insulin resistance.[1] Hirsutism is the term used for androgen-sensitive male-pattern hair growth in girls.[2] The most common cause of hirsutism in adolescent girls is PCOS, and it is seen in 5%-10% of women of reproductive age.[3] Insulin resistance and increased insulin level have been shown to be the etiology of hyperandrogenism. The treatments used to date vary according to the source of hyperandrogenism and the clinical condition of the patient. Birth control pills, metformin, antiandrogens such as spironolactone and finasteride are some of these treatments.[4]

Highlights

- Hyperandrogenism causes chronic anovulation in adolescent girls and causes the development of many systemic diseases.
- Vitamin D supplementation is effective in curing some diseases. There are studies showing that androgen levels decrease with the addition of vitamin D to metformin.
- The current study shows that long-term and adequate dose of vitamin D is required to see this effect.

Obesity is the most common cause of insulin resistance and hyperandrogenism. Therefore, weight loss may be the first line of treatment for women with hyperandrogenism.[4] Metformin is the most commonly used drug for treating type 2 DM (Diabetes mellitus). This drug increases glucose uptake by peripheral tissues while reducing peripheral insulin levels and fatty acid oxidation. Additionally, various effects of this drug have reported such as, regulating ovulation, weight loss, lowering circulating androgen levels and reducing the risk of miscarriage in patients with PCOS.[5]

In recent studies, vitamin D has been one of the nutritional factors recommended for treating PCOS. Vitamin D, which belongs to the family of steroid hormones, is fat-soluble. Serum 25(OH)D is the best indicator of vitamin D level. Vitamin D (25(OH)D) level <20 ng/ml is defined as severe deficiency, 20-30 ng/ml as deficiency, 30-100 ng/ml level as adequacy, and more than 100 ng/ml level as toxicity.[6] It has been suggested that gene transcription is regulated through vitamin D receptors (VDRs) found in various tissues, including the skeletal system, parathyroid glands, heart, immune system, and ovaries.[3] Vitamin D deficiency appears to be associated with increased parathyroid hormone (PTH) level, PCOS, ovulatory infertility, and high testosterone.[3] Additionally, it has been reported that vitamin D supplementation significantly reduces the serum total testosterone level.[3] In our study, the files of adolescent female patients diagnosed with hyperandrogenism and given outpatient treatment were reviewed retrospectively. Our aim in this study is to show the relationship between vitamin D treatment and androgen levels in addition to metformin treatment. It is important because it is the first study conducted in adolescents in our country.

Material and Method

The study was carried out with the permission of Süleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee (Date: 20.12.2017, Decision No: 226). Between December 2017 and September 2018 forty-five female patients were selected who applied to our endocrine outpatient clinic with complaints such as increased hair growth, menstrual irregularity, acne, male pattern hair loss and diagnosed with hyperandrogenism. File information was reviewed retrospectively.

Patients with systemic disease and using medication and vitamin therapy were excluded from the study. The height and weight of the patients were recorded according to the file information. Body mass index (BMI) was calculated with the formula body weight (kg) / height² (m²). Ferriman Gallwey scoring was used in patients with hirsutism, and patients with a score of 8 and above were considered hirsutism. Patients who did not want pelvic ultrasound were excluded from the study. Patients with normal ultrasound results were included. Glucose, vitamin D, insulin, Homa-IR (homeostatic model evaluation of insulin resistance), ALT (alanine aminotransferase), LDL (low-density lipoprotein), HDL (high-density lipoprotein), triglyceride, FSH (follicle stimulating hormone), LH (luteinizing hormone), estradiol, DHEAS (dehydroepiandrosterone sulfate), androstenedione, free testosterone, total testosterone and SHBG (sex hormone binding globulin) values were recorded. The total testosterone of the patients was >55 ng/dl. A Homa-IR above 4 was considered insulin resistance (Homa-IR: Fasting insulin (µu/ml) x fasting plasma glucose (mg/dl) /405).[7] The patients were divided into 3 groups according to the treatment they received (n=15). Group M was given 850 mg/day of metformin. Metformin-vitamin D 15 drops/day (2 000 IU) was given to the MdD group. Half of the metformin-vitamin D ampoule (150,000 IU/month) was given orally to the MsD group. After 8 weeks, biochemical and hormonal parameters were compared statistically.

Statistical Analysis

SPSS 23.0 program was used for statistical analysis in the study. Descriptive statistics were given as mean±standard deviation. The Kolmogorov-Smirnov test was used to examine the normal distribution of variables. Changes between the three groups were compared using the LSD post hoc pairwise comparison method using one-way analysis of variance. Significance level was set as $p<0.05$.

Results

File information about 270 female patients aged between 12 and 18 who were diagnosed with hyperandrogenism was analyzed. Among these patients, 90 (33%) patients due to thyroid hormone disorder, 62 (22%) patients due to diabetes, 20 (7.4%) patients due to non-classical congenital adrenal hyperplasia (non-classical CAH), 4 (1.4%) patients due to prolactinemia, 49 (18%) patients

who did not meet the study criteria and/or did not have sufficient file information was not included in the study (**Figure 1**). The study was conducted in 45 (16.6%) subjects who met the inclusion criteria.

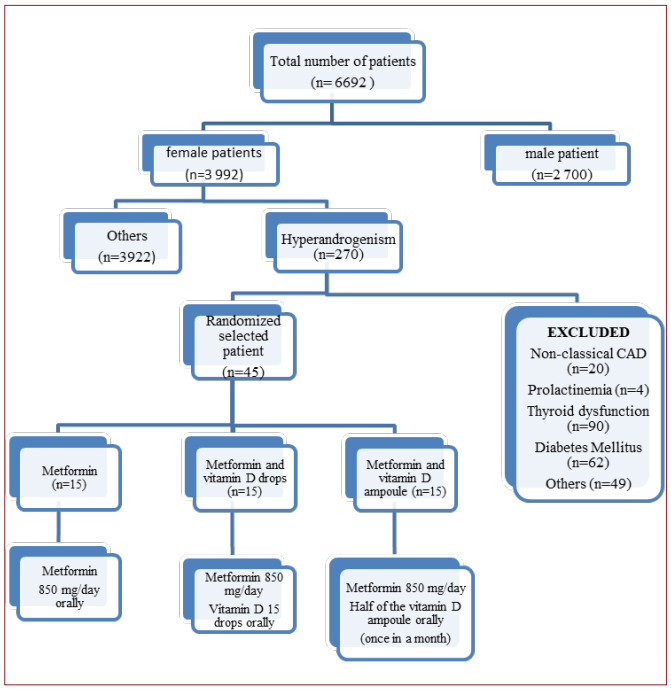

Figure 1. Summary of the patient follow-up chart

There was no significant difference between the mean age, weight and height of the groups before the study (p>0.05). The BMI of the M and MdD groups were significantly different from each other at the beginning of the study (p<0.01). However, after 8 weeks of treatment, there was no significant correlation between the BMIs of the groups (p>0.05) (**Table 1**).

Severe vitamin D deficiency (<20 ng/ml) was observed in 68.8% of all patients, vitamin D deficiency (20-30 ng/ml) in 26.6%, and vitamin D adequacy (>30 ng/ml) was observed in the remaining 4.4%. Severe vitamin D deficiency (<20 ng/ml) was observed in 68.8% of all patients, vitamin D deficiency (20-30 ng/ml) in 26.6%, and vitamin D adequacy (>30 ng/ml) was observed in the remaining 4.4%. While the mean total testosterone of those with severe vitamin D deficiency was 70.4 at the beginning of the study, it was 60.5 at the end of the study. SAI mean decreased from 10.8 to 10.2. The DHEAS average increased from 277 to 279. The mean total testosterone of those with vitamin D deficiency decreased from 70.7 to 57.1 with treatment. While the mean SAI was 9.8, it became 7.9 with treatment. The DHEAS average increased from 315 to 348. The mean total testosterone of those with adequate vitamin D levels decreased from 66.8 to 64.8. SAI average decreased from 4.2 to 4.9. The DHEAS average increased from 340 to 346. In the initial data of the study, there was no significant difference between the serum vitamin D levels of the groups (**Table 2**).

At the end of the 8-week treatment, a higher serum vitamin D level was observed in the MsD group compared to the MdD group. In our study, no significant correlation was found between vitamin D level and total testosterone, insulin, glucose, lipid profiles, FSH, LH, estradiol and DHEAS (**Table 3**).

Table 1
Physical characteristics of the patientsa

	M[b] (n=15)	MdD[d] (n=15)	MsD[c] (n=15)	p
Age (y)	14.8±1.86	15.7±153	16.2±1.29	0.67
Height (cm)	158.6±7.50	162.3±4.57	160.8±7.08	0.99
Weight (kg)	62.09±15.06	82.2±15.88	74.4±18.87	0.90
BMI (kg/m²)	24.50±5.05	31.07±5.40*	28.28±6.82	0.01
BMI (kg/m²) difference	-0.25±1.61	-0.10±1.23	-0.11±1.39	0.90

[a]Data mean±standard deviation, [b]Group receiving 850-mg metformin orally daily, [c]Group who took 850 mg metformin and half of the vitamin D ampoule (150 000 IU) once a month orally, [d]Group taking 850-mg metformin and 15 drops (2 000 IU) of vitamin D orally daily, *Statistical difference between M and MdD

Table 2
Effects of metformin and vitamin D supplements on glucose metabolism, lipid profile and androgen levels in adolescents with hyperandrogenisma (Primary data of the study)

	M[b] (n=15)	MsD[c] (n=15)	MdD[d] (n=15)	p
Vitamin D (ng/mL)	22.87±6.93	15.05±7.42	14.42±3.76	0.04
Glucose (mg/dL)	98.59±15.36	91.81±11.21	92.75±8.55	0.12
ALT (U/L)	19.78±11.45	19.62±13.94	19.94±9.28	0.95
Insulin (µU/mL)	33.48±7.30	35.28±14.73	32.23±11.35	0.25
HOMA-IR	8.16±2.34	8.25±4.41	7.35±2.69	0.09
HDL (mg/dL)	52.46±15.11	49.26±9.64	46.69±7.44	0.35
LDL (mg/dL)	86.60±23	94.23±22.98	97.95±40.54	0.33
Triglyceride (mg/dL)	116.23±54.80	105.35±53.32	123.25±63.26	0.45
FSH (mIU/mL)	6.18±1.87	6.47±2.33	4.98±1.52	0.16
LH (mIU/mL)	9.73±6.46	9.00±4.73	9.55±6.97	0.38
Estradiol (pg/mL)	78.13±47.78	75.07±61.70	69.87±41.15	0.68
DHEAS (ug/dL)	304.74±125	331.12±143	290±137	0.45
ANDR (ng/mL)	1.81±0.81	2.62±0.89	2.29±1.26	0.97
S.Testosterone (pg/mL)	2.12±1.11	2.52±0.68	2.25±0.74	0.15
T.Testosterone (ng/dL)	70.63±11.90	69.87±14.81	71.22±12.85	0.84
SHBG (nmol/L)	37.69±29.49	28.48±15.69	32.67±27.41	0.32

[a]Data mean±standard deviation, [b]Group receiving 850-mg metformin orally daily, [c]Group who took 850 mg metformin and half of the vitamin D ampoule (150 000 IU) once a month orally, [d]Group taking 850-mg metformin and 15 (2 000 IU) of vitamin D orally daily, ANDR: Androstenedione (ng/mL), ST: Free testosterone (pg/mL), TRG: Triglyceride (mg/dL), ESTR: Estradiol (pg/mL)

Table 3
The effects of metformin and vitamin D supplements on glucose metabolism, lipid profile and androgen levels in adolescents with hyperandrogenisma

	Latest data of the study				Differences between first and last data			
	M[b] (n=15)	MdD[c] (n=15)	MsD[d] (n=15)	p	M[b] (n=15)	MdD[d] (n=15)	MsD[c] (n=15)	p
Vitamin D (ng/mL)	23.58±7.95	20.34±6.32	25.04±10.90	0.31	0.70±8.76	5.91±4.67*	9.99±13.34	0.03
Glucose (mg/dL)	91.77±7.33	92.42±7.51	87.88±6.83	0.19	-6.83±15.79	-0.33±8.02	-3.93±12.23	0.36
ALT (U/L)	18.83±12.81	18.45±7.09	21.57±14.70	0.74	-9.95±9.13	-1.49±8.19	1.94±9.53	0.53
Insulin (µU/mL)	22.11±10.34	23.78±7.08	22.31±9.06	0.85	-11.38±9.66	-8.45±11.98	-12.98±15.74	0.61
HOMA-IR	5.06±2.46	5.48±1.82	4.89±2.20	0.75	-3.11±2.81	-1.88±2.80	-3.37±4.54	0.46
HDL (mg/dL)	51.36±9.93	49.89±8.19	52.43±12.61	0.79	-1.10±10.77	3.20±7.10	3.16±5.96	0.26
LDL (mg/dL)	89.08±14.82	98.75±41.38	96.44±26.32	0.64	2.48±25.90	0.79±20.76	2.20±13.58	0.97
Triglyceride (mg/dL)	118.45±60.55	116.35±73.98	113.69±50.28	0.97	2.22±47.60	-6.91±34.17	8.34±54.95	0.66
FSH (mIU/mL)	6.02±2.70	4.80±2.10	5.63±2.55	0.38	-0.16±2.68	-0.19±1.91	-0.84±3.58	0.75
LH (mIU/mL)	7.78±5.30	7.94±5,58	6.09±3,55	0.52	-1.96±5.95	-1.62±5.18	-2.91±5.69	0.80
Estradiol (pg/mL)	72.93±62.03	78.73±45.83	73.87±73.14	0.96	-5.20±52.44	8.87±67.64	-1.20±54.81	0.79
DHEAS (ug/dL)	335.77±149.32	275.64±112.89	341.25±133.63	0.33	31.03±79.25	-14.45±106.10	10.13±88.85	0.40
ANDR (ng/mL)	1.51±0.77	2.20±1.34	2.37±0.97	0.73	-0.30±0.80	-0.09±1.98	-0.26±1.44	0.92
S.Testosterone (pg/mL)	2.07±0.87	2.15±0.76	2.20±1.22	0.93	-0.05±0.73	-0.11±0.52	-0.33±1.36	0.69
T.Testosterone (ng/dL)	62.75±17.45	59.62±17.57	55.76±27.87	0.67	-7.89±21.40	-11.61±13.79	-14.12±16.17	0.61
SHBG (nmol/L)	41.78±31.34	36.04±33.23	59.62±70.36	0.38	4.08±30.07	3.37±28.96	31.14±63.68	0.15

[a]Data mean±standard deviation, [b]Group receiving 850-mg metformin orally daily, [c]Group who took 850 mg metformin and half of the vitamin D ampoule (150 000 IU) once a month orally, [d]Group taking 850-mg metformin and 15 drops (2 000 IU) of vitamin D orally daily

Although there was no statistically significant relationship between vitamin D and total testosterone levels in our MsD and MdD groups, a slight decrease in serum total testosterone levels was observed in the groups. Additionally, there was a positive correlation between total testosterone and ALT (r=0.58, p=0.02) in our group-given metformin-vitamin D drops. There was a positive correlation between SHBG and HDL levels in all three groups (p<0.05). There was a positive correlation between vitamin D and SHBG levels in the metformin group (r=0.65, p=0.009) and a negative correlation between SHBG level and androstenedione (r=-0.56, p=0.02) (**Table 4**). This consistent result is a desirable finding for treating hyperanrogenism, reaffirming the importance of high SHBG and low androstenedione levels.

A negative correlation was observed between insulin and LDL (r=-0.68, p=0.005) and BMI (r=-0.58, p=0.02) in the metformin group. A positive correlation was observed between insulin and triglycerides in the MsD and MdD groups (p<0.05) (**Table 4**) (**Figure 2**). There was a slight decrease in fasting insulin level and BMI in all 3 groups, but this decrease was not statistically significant.

Table 4
Statistically significant Pearson correlations between hormone and metabolic parameters in M, MsD, MdD groupsa

	M[a] (n=15)		MdD[b] (n=15)		MsD[c] (n=15)	
	r	p	r	p	r	p
Vitamin D						
SHBG	0.65	0.00	0.14	0.60	0.17	0.53
T. testosterone						
ALT	-0.22	0.43	-0.05	0.85	0.58	0.02
Estradiol	0.66	0.00	0.63	0.01	0.05	0.84
SHBG						
Vitamin D	0.65	0.009	0.14	0.60	0.17	0.53
Triglyceride	0.61	0.01	0.58	0.02	0.180	0.51
HDL	0.52	0.04	0.66	0.00	0.54	0.03
Androstenedion	-0.56	0.02	-0.43	0.10	0.05	0.85
Insulin						
Triglyceride	-0.36	0.18	0.64	0.01	0.54	0.03
Glucose	0.36	0.18	0.56	0.02	-0.05	0.83
LDL	-0.68	0.005	-0.33	0.22	-0.11	0.69
BMI	-0.58	0.02	0.22	0.42	-0.14	0.60

[a]Data mean±standard deviation, [b]Group receiving 850-mg metformin orally daily, [c]Group who took 850 mg metformin and half of the vitamin D ampoule (150 000 IU) once a month orally, [d]Group taking 850-mg metformin and 15 drops (2 000 IU) of vitamin D orally daily

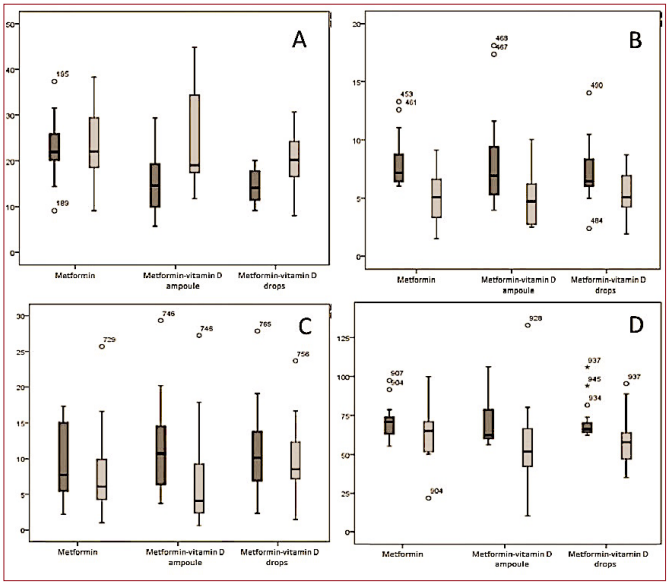

Figure 2. Comparisons of the groups

Discussion

Recent studies suggest that low vitamin D levels may be the primary factor in the initiation and progression of PCOS.[8] Therefore, dietary intake of vitamin D is thought to help restore the menstrual cycle in women with PCOS.[8] This is the first study in our country to examine vitamin D levels and androgen parameters in adolescents to the best of our knowledge.

Previous studies have addressed the effects of vitamin D and calcium supplementation on endocrine, inflammation and oxidative stress markers in women with PCOS who are vitamin D deficient.[9,10] Additionally, Rashidi et al. showed that the combined use of calcium-vitamin D and metformin in women with PCOS was more effective in

regulating the menstrual cycle and follicle maturation than the use of either drug alone.[8] Razavi et al. found that 8 weeks of vitamin D, vitamin K, and calcium supplementation in women diagnosed with PCOS in 2016 significantly reduced serum free testosterone and DHEAS compared to placebo, while not affecting other hormonal profiles.[10] In this study, we could no observe a significant decrease in total testosterone, free testosterone and DHEAS following metformin-vitamin D treatment for 8 weeks in the M, MsD, and MdD groups. However, total testosterone was positively correlated with ALT (r=0.58, p=0.02) in the MsD group. We can explain this situation by the fact that the high ALT level seen in women with PCOS is related to the effect of increased androgen level independent of obesity, insulin resistance and dyslipidemia.[11]

Vitamin D appears to play an important role in the secretion of insulin from pancreatic β cells and the stimulation of insulin receptors.[12] In some studies in patients with PCOS an inverse correlation was found between vitamin D levels and insulin resistance.[13] Mishra et al. showed in 2016 that low vitamin D is a risk factor for impaired glucose tolerance, insulin resistance, and type 2 DM.[14] However, Selimoğlu et al. showed that HOMA-IR decreased with a single dose of 300,000 IU vitamin D supplementation for 3 weeks in individuals with PCOS, but in this case, fasting insulin and glucose concentrations were not affected.[15] Garg et al. found that vitamin D supplementation given 4000 IU/day for 6 months did not have a significant effect on insulin levels in women with PCOS.[16] Although our study showed similar results, we found that vitamin D supplementation did not affect fasting insulin level, glucose concentration and HOMA-IR. In our study, adequate vitamin D level (>30 ng/dl) was achieved in only 4% of our patients after 8 weeks of vitamin D treatment. We predict that a more significant effect on insulin and androgen levels will occur with long-term vitamin D supplementation. We attributed this hypothesis to the study by Menichini et al. in which they found positive effects of high-dose vitamin D (4000 IU/day) administered for at least 12 weeks on fasting blood glucose, insulin sensitivity, hyperlipidemia, and fertilization in patients with PCOS.[17]

Vitamin D stimulates aromatase activity, which is effective in the conversion of testosterone to estrogens in granulosa cells, which causes a balance in androgen and estrogen levels in patients with PCOS.[18] In a study by Azadi-Yazdi et al. in 2017 on women with PCOS, it was revealed that vitamin D supplementation significantly reduced serum total testosterone level and did not affect SHBG and free testosterone levels.[3] In our study, there was a positive correlation between vitamin D and SHBG in the M group (p=0.009). This significant result we obtained in the group not given vitamin D can be explained by the fact that the vitamin D level of the M group was higher than the other groups at the beginning of the study. In support of this situation, in a study by Zhao et al. in 2017, low vitamin D concentration was associated with low SHBG and high free testosterone levels in men and women; showed that it was associated with low estradiol and high DHEA levels in women.[19]

In some studies examining the relationship between vitamin D deficiency and metabolic syndrome, it has been shown that vitamin D supplementation contributes to the improvement of metabolic syndrome in patients.[20] Hahn et al. found a positive correlation between vitamin D and HDL cholesterol (r=0.312, p<0.05).[21] Grunwald et al., on the other hand, did not find any relationship between vitamin D deficiency and metabolic parameters in obese children.[22] In a study by Foroozanfard et al. in 2017, they stated that in patients with PCOS, serum triglycerides, VLDL, LDL and total cholesterol ratios decreased significantly with 4000 IU/day vitamin D supplementation compared to 1000 IU/day vitamin D supplement given for 12 weeks. However, no significant effect was shown on HDL-cholesterol levels.[23] In our study, there was a significant relationship between insulin and triglycerides in the group-given metformin-vitamin D stoss treatment (r=0.54, p=0.03). There was a positive correlation between SHBG and HDL levels in all three groups (p>0.05). In a study by Temizsiz et al. in 2017, it was stated that the decrease in SHBG level is associated with obesity, hyperinsulinemia and dyslipidemia. They also found a positive relationship between SHBG and HDL.[24]

In adolescents with PCOS, increased total-LDL cholesterol and triglyceride levels may increase the risk of cardiovascular disease.[25] Therefore, the treatment of associated cardiovascular risk factors, including dyslipidemia, should be included in the routine healthcare program of patients with PCOS. Because vitamin D can reduce lipid profiles by increasing insulin sensitivity.[26] We think that this will lead to positive results in terms of reducing cardiovascular diseases accompanied by high triglyceride levels.

Conclusion

Significant correlations were found in androgen and lipid parameters with the addition of vitamin D to 8 weeks of metformin treatment. We think that the positive correlation between vitamin D and SHBG will have a positive effect on ensuring ovulation and keeping the androgen level within normal limits. Depending on the positive correlation between insulin and triglycerides, the decrease in insulin level may contribute to the improvement of dyslipidemia by reducing the triglyceride level. Additionally, the significant relationship between total testosterone and ALT may have a protective effect on liver functions by decreasing the androgen level and decreasing the ALT level. However, long-term studies are needed to support our results.

Author Contributions: Esranur Cig: design of the study, retrospective collection of data, statistical analysis, writing, methodology; Muge Atar: investigation; M.Ozgur Pırgon: design of the study, reviewing, editing. All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Süleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee (Date: 20.12.2017, Decision No: 226).

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Informed Consent: Informed consent was obtained from the parents of the patients.

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Case Report

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Anatomically Corrected Malposition of the Great Arteries with Atrioventricular Concordance and Left Juxtaposition of the Atrial Appendages

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Abstract

Anatomically corrected malposition of the great arteries is a rare cardiac malformation. In this condition the great arteries are abnormally related to each other and to the ventricles, but arise from the anatomically correct ventricles. In patients with atrioventricular concordant and the absence of associated anomalies, the circulation is physiologically normal. However, ventricular septal defect and right ventricular outflow tract stenosis are the most common accompanying pathologies that require surgical intervention. Here, we present a 9-day-old female with anatomically corrected malposition of the great arteries with wide atrial septal defect, mild right ventricular outflow tract stenosis, left juxtaposition of the atriums, and wide malalignment subaortic ventricular septal defect that required aortotomy to close the defect.

Keywords: Anatomically corrected malposition of the great arteries, echocardiography, juxtaposition, ventricular septal defect.

Introduction

Anatomically corrected malposition of the great arteries (ACMGA) is a rare form of congenital heart disease in which the arterial trunks arise above the anatomically correct ventricles but are abnormally related to each other and to the ventricles.[1] There may be atrioventricular (AV) concordant or discordant, but there should be ventriculoarterial (VA) concordant. The aorta arises from the morphological left ventricle and the pulmonary trunk arises from the morphological right ventricle. In this situation, the aorta is located anterior, which may left or right of the pulmonary trunk. Clinical presentation and management of ACMGA relate to associated anomalies. Ventricular septal defect (VSD), right ventricular outflow tract obstruction (RVOTO), right ventricle (RV) hypoplasia, juxtaposed atrial appendage, and right aortic arch are the most associated anomalies.[2,3] In patients with atrioventricular concordant and the absence of associated anomalies, the circulation is physiologically normal.[2]

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In this article, we present a patient who was diagnosed with ACMGA with large malalignment VSD, large secundum atrial septal defect (ASD), left juxtaposition of the atria, and mild RVOTO, whose VSD margins can only be approached through aortotomy.

Case Report

A 9-day-old female patient was consulted for a murmur following for hyperbilirubinemia in the neonatal intensive care unit. Her general condition was good, respiratory rate was 42 / min, heart rate was 148 / b.p.m, oxygen saturation was 98%. A 2/6 systolic murmur was in the pulmonary focus. Other system examinations were normal. Electrocardiography demonstrated normal sinus rhythm, normal axis and incomplete right bundle branch block. Her telecardiogram was normal with cardiac index within referral range. Transthorasic echocardiography showed atrial situs solitus (S); the right atrium was drained to the right sided morphological right ventricle and the left atrium to the left sided morphological left ventricle (D); the aorta arose morphological left ventricle and pulmonary trunk arose morphological right ventricle in a side by side position (AV-VA concordant) with the aorta was anterior leftward (L). The accompanying pathologies were wide subaortic malalignment VSD, wide secundum ASD, thin patent ductus arteriosus (PDA), mild RVOTO with estimate gradient of 30 mmHg, left juxtaposition of the atriums and right aortic arch. The diagnosis of ACMGA (S.D.L.) with subaortic malalignment VSD and mild RVOTO was therefore made (**Figure 1 a,b**). Decongestive treatment was given when she was one month old and followed up until the age of four months. Surgery was decided because the patient did not gain enough weight (4,92 kg, <3%) and had symptoms of heart failure. In addition to the echocardiographic findings, aberrant innominate artery was observed in the preoperative computed tomography angiography. (**Figure 2 a,b,c**). During the operation, median sternotomy incision was made to reach the mediastinal structures. Thymectomy performed. After pericardial incision, morphological findings of ACMGA were confirmed (**Figure 2 d**). Aortic bicaval cannulation performed. Patent ductus arteriozus ligated first then cardiopulmonary bypass institued; and antegrad cold blood cardioplegia delivered. After diastolic arrest right atriotomy performed. Secundum type ASD was clearly seen but VSD was unable to localized. The main pulmonary artery was then opened to achieving more satisfactory visualization of the VSD margin. However, the VSD could not be seen through the pulmonary artery approach. Aortotomy was performed, then the leaflets of the aortic valve were retracted. The VSD was completely seen under the right coronary cusp of the aortic valve.

A polytetrafluoroethylene (PTFE) patch material was sutured to the margins of the VSD through the aortotomy approach. Aortopexy were performed to aberrant innominate artery pressing trachea anterior. Since the RVOTO was mild and pulmonary outflow tract was normal, its not intervened. Postoperative echocardiography showed an unobstructed pathway from the LV to the aorta, with no residual shunt and no significant RVOTO. After an uneventfull recovery period, patient discarhed in stable condition with sinüs rhythm at postoperative day 5. Consent was obtained from the patient's parent for this case study.

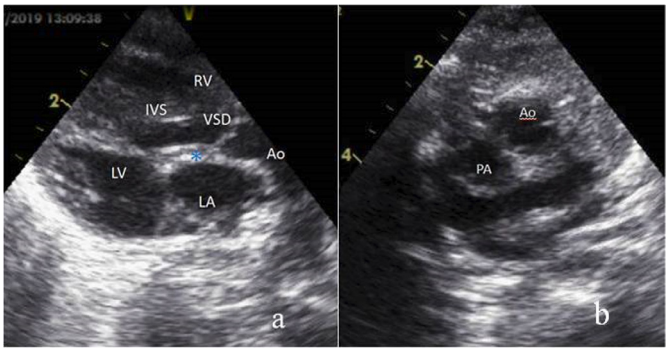

Figure 1. a) Transthorasic echocardiography showed subaortic malalignment ventricular septal defect and aorta, arised from left ventricle, in five chamber view, **b)** aorta located anterior leftward in short axis view.

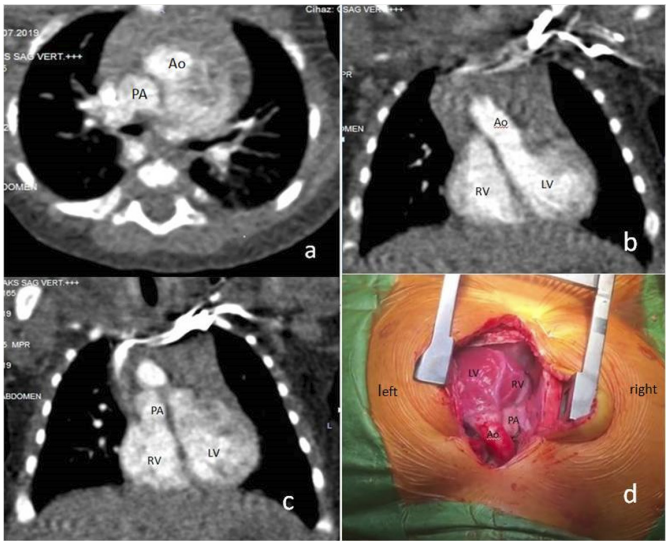

Figure 2. a) Computed tomography anjio showed aorta located anterior leftward, **b)** aorta arised from left ventricle, **c)** pulmonary artery arised from right ventricle, **d)** aorta, located anterior leftward, arised from left ventricle and pulmonary artery located posterior, arised from right ventricle in the surgical image.

Discussion

Anatomically corrected malposition of the great arteries was first reported by Theremin in 1895, later characterized by Van Praagh et al. in 1975.[4] In contrast to transposition of the arterial trunks, which cross the opposite side of the septum and arise from the anatomically inappropriate ventricle, in this condition parallel arterial trunks are normally connected to their appropriate ventricles (VA concordant).[5] It is divided to 4 types based on atrium, ventricle and great arteries segmental analysis. According to Van Praagh's symbolic terminology, there are two types of situs solitus, type 1: (S.D.L.), type 2: (S.L.D.) and two types of situs inversus, type 3: (I.L.D.), type 4: (I.D.L.). Of these pathologies, type 1 and type 3 have normal corrected physiology, while type 2 and type 4 have transposition physiology.[4] According to Ali et al.

review, 78% of the cases are (S.D.L.) and the others are 17.5% (S.L.D.), 4.5% (I.D.L.) types in biventricular ACMGA.[2] In addition to biventricular pathologies, the combination of concordant VA connections with parallel arterial trunks can be found in the setting of isomeric atrial appendages, double inlet left ventricle, and in absence of the right atrioventricular connection.[6] Arterial trunks may also be VA concordat when the morphologically right ventricle was itself left sided, or in the setting of mirror-imaged atrial arrangement but with the morphologically right ventricle in the right-sided position. Thus, the pulmonary trunk can be located on the left as in the normal heart, or on the right as expected for the mirror-imaged atrial arrangement. So, it can be claimed that only the ventricular arrangement is abnormal. Therefore, these unusual situations can be described as isolated ventricular inversion or isolated atrioventricular discordant.[6]

The clinical presentation and management of ACMGA depends on the associated anomalies, such as VSD, ASD, PDA and ventricular outflow tract stenosis (subaortic or subpulmonic). The most common concomitant anomaly is VSD (90%), and the most frequent indication of the surgery is also VSD. Pulmonary stenosis (valvular and/or) often accompanies VSD (59%), and relieve of the pulmonary stenosis may also be required with VSD closure. The other associated anomalies are: 62.5% of the cases have left juxtaposition, 15% of the cases have aortic stenosis.[2] In our patient, there were subaortic malalignment VSD, wide secundum ASD, left juxtaposed appendage, right aortic arch and mild pulmonary stenosis. At the age of four months, VSD and ASD was surgically closed due to growth retardation; pulmonary stenosis was not intervened because it was mild. When S.D.L. is present, the surgical success rate is 92%. However, when AV discordant or hypoplastic RV present, success rate is only 29%.7 Some syndromes such as VACTERL[8] and Goldenhar Syndrome[9] were reported to be associated with ACMGA. However, there was no accompanying syndrome in our patient.

Awashty et al.[10] reported that in their patient with ACMGA (S.D.L.) and DORV the presence of subaortic conus (infundibulum) along with the left juxtaposition of the right atrial appendage resulted in the inability to visualize the VSD from either the right atrium or pulmonary artery or even through a ventriculotomy approach, thus had been necessitated a transaortic approach. In our patient, like Awashty et al.,[10] we could not reach from the right atrium or pulmonary artery; the VSD could be fully visualized in its entirety only by looking down through the aortic valve orifice.

Conclusion

Because of ACMGA is a rare entity, it can be confused with congenitally corrected transposition of the great arteries and transposition of the great arteries. The segmental approach will help to evaluate the morphology of the heart before surgery and to distinguish it from other similar pathologies. This case also highlights the need to recognize the value of the transaortic approach to VSD, in the segmental anatomy that exists with the left juxtaposition of the atriums in ACMGA (S.D.L.) as repotred earlier.

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

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

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Journal of Pediatric Academy

Image Corner

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Pediatric Posttraumatic Cystic Bone Lesion

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Pediatric posttraumatic cystic bone lesion, also known as fracture cyst, transient fatty cortical defect, transient post-fracture cyst is an uncommon complication of fractures in children. Approximately 30 cases were reported in the literature. Typically, it occurs in 2-4 months following minor traumatic fractures. It usually occurs at distal radius following a greenstick, buckle or torus fracture.[1] Intramedullary fat leakage through the damaged bone cortex and its capture in subperiosteal area has been proposed in etiology. On radiographs, it is seen as a well-circumscribed, non-expansile, subcentimeter, radiolucent lesion that is located in cortex, close to the former fracture site. Computerized tomography (CT) shows well-defined, intracortical, fatty density and MRI may show signal loss on fat suppressed sequences.[2] It may be seen in multiple locations. These lesions are asymptomatic and do not cause fever or pain. Differential diagnosis may contain unicameral bone cyst, non-ossifying fibroma, eosinophylic granuloma, osteomyelitis. No treatment is required, as they resolve spontaneously in 1 to 3 years.[2,3]

A 4-year-old girl presented to emergency department with left wrist pain after trauma. Radiographs demonstrated a torus fracture of the distal radius (**Figure 1**). At the third month following the trauma, a control radiograph is obtained. In the radiograph, a radiolucent lesion close to the former torus fracture site is noticed (**Figure 2**). Then, CT is performed for further examination (**Figure 3**). CT demonstrated cortical, well-circumscribed non-expansile subcentimeter lesion.

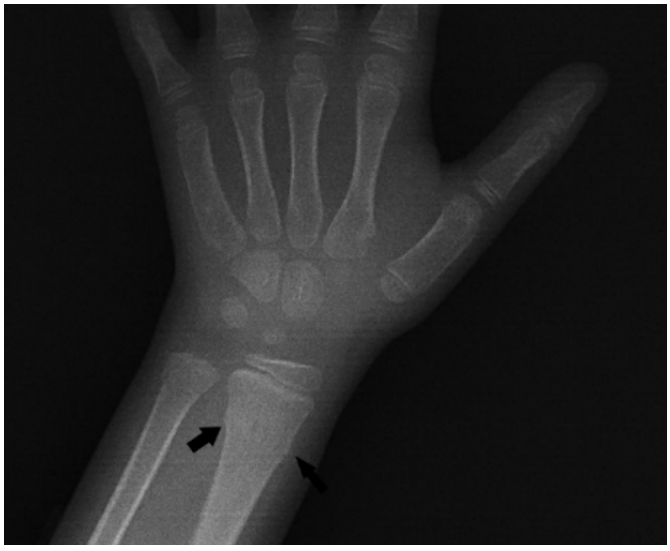

Figure1: Radiographs of the left wrist at the time of injury. A torus fracture of the distal radius (arrows) is seen.

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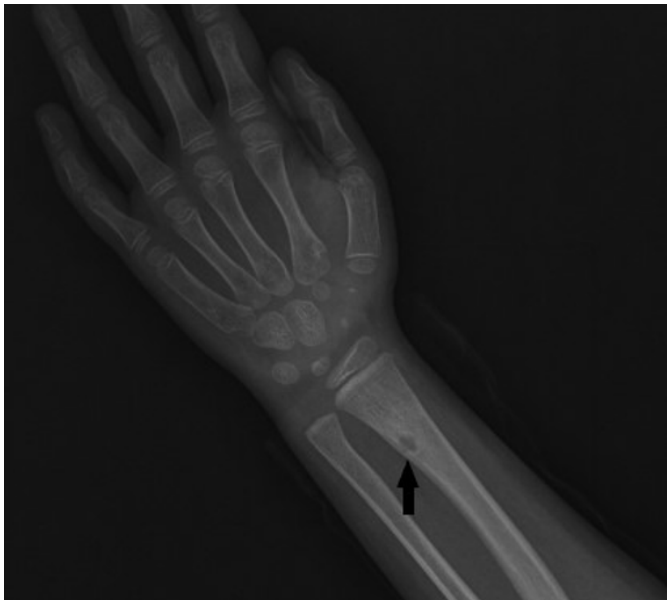

Figure 2. Control radiograph, 3 months after trauma. A well-circumscribed radiolucent lesion in the cortex of distal radius at the former fracture site.

The patient was seen two and a half months later. Radiography showed fading of the lesion. No further follow-up is needed. It is essential to recognize this lesion to prevent unnecessary further diagnostic examinations or even invasive diagnostic procedures.

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

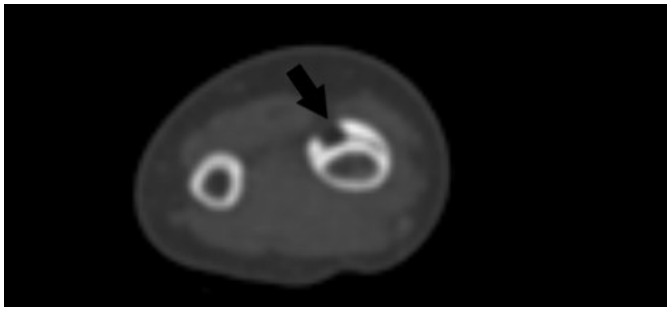

Figure 3: CT appearance of the posttraumatic cystic bone lesion. A well-circumscribed cortical lesion with fatty density (arrow) is seen.

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