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Original Article

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Evaluation of hemogram parameters in patients with atopic dermatitis

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ABSTRACT

Aims: This study aimed to evaluate the hemogram parameters of patients with atopic dermatitis (AD) and contribute to the existing literature.

Methods: This cross-sectional study retrospectively analyzed data from pediatric patients diagnosed with AD, who presented to the Pediatric Allergy and Immunology outpatient clinic at Ümraniye Training and Research Hospital between January 1, 2024, and August 15, 2024. The sociodemographic characteristics, hemogram parameters, total IgE values, allergy history, and allergy test results of the patients were evaluated. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammatory response index (SIRI), neutrophil/lymphocyte/platelet ratio (NLPR), and pan-immune-inflammation value (PIV) were calculated. Allergen-specific IgE measurements were performed using the ImmunoCAP method, and skin prick tests were conducted for food and inhalant allergens. The severity of AD was classified as mild or moderate-to-severe based on the potency of the topical corticosteroids used by the patients. Statistical analyses were performed using SPSS version 29.0.

Results: A total of 346 patients diagnosed with AD were included in the study. Among the patients, 53.8% were male, and the median age was 32.5 months. Mild AD was identified in 46.5% of the patients, while 53.5% had moderate-to-severe AD. Although sensitization to house dust mites, cats, eggs, and nuts was more frequent in patients with moderate-to-severe AD, no statistically significant difference was found between allergen sensitization and AD severity. Eosinophil count and eosinophil-lymphocyte ratio (ELR) were significantly higher in moderate-to-severe AD patients compared to those with mild AD ($p=0.008$ and $p=0.004$, respectively). No significant difference was found for other hemogram parameters and inflammatory markers. Patients with allergen sensitization had significantly higher WBC, basophil, eosinophil counts, and total IgE levels ($p<0.05$).

Conclusion: This study evaluated the relationship between hematological parameters and allergen sensitization in AD patients. Eosinophil count and ELR were significantly elevated with increasing AD severity. However, NLR, SII, SIRI, NLPR, and PIV were not associated with AD severity. Patients with allergen sensitization had significantly higher WBC, eosinophil, basophil counts, and total IgE levels. Our findings suggest that eosinophil count and total IgE levels may serve as predictive markers for AD severity and allergen sensitization. Routine measurement of these parameters could offer a practical approach in determining AD severity and allergen sensitization. Further research is needed to clarify the clinical significance of other hematological parameters.

Keywords: IgE, eosinophil, inflammation

INTRODUCTION

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease characterized by inflammation.[1] It is a multifactorial disease influenced by genetic and environmental factors.[2] While 80% of cases are seen in infancy or childhood, it can also appear during adolescence. The prevalence in children ranges from 2.7% to 20.1%, while in adults, it varies between 2.1% and 4.9%.[3,4] AD is characterized by itching, eczema, and sensitive, dry skin.[5] The acute phase is predominantly mediated by the Th2 pathway, while both Th1 and Th2 pathways are involved in the chronic phase. Though its exact cause is not fully understood, genetic and environmental factors are believed to play a role.[6,7] AD is

often associated with other allergic conditions such as food allergies, allergic asthma, and rhinoconjunctivitis.[8] Treatment options include topical corticosteroids, calcineurin inhibitors (tacrolimus and pimecrolimus), and phosphodiesterase 4 inhibitor crisaborole. In more severe cases, cyclosporine A, methotrexate, azathioprine, mycophenolate mofetil, and JAK inhibitors are recommended.[9] Disruption of the skin barrier plays a crucial role in the disease's pathophysiology, with IL-4, IL-5, IL-12, and IFN-gamma released in response to Th2 and Th1 activation.[10-13] Studies have shown elevated levels of total IgE, eosinophils, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and eosinophil/lymphocyte ratio (ELR) in AD patients compared to control groups.[14] In AD, an increase in the number of eosinophils in the blood and tisses may be observed.[15]

Systemic immune-inflammation index (SII), systemic inflammatory response index (SIRI), and pan-immune-inflammation value (PIV) are new markers used to evaluate inflammation.[16,17] The neutrophil-lymphocyte-platelet ratio (NLPR) was calculated as (neutrophilx100)/(lymphocyte×platelet). The pan-immune inflammation value was also calculated as (neutrophil×platelet×monocyte)/lymphocyte. The SIRI=(neutrophil count×monocyte count)/lymphocyte count, reflecting increased inflammation and decreased immune response. SII and SIRI have been studied as markers and predictors in other diseases and conditions, such as different types of cancer or cardiovascular events.[18,19] The pan-immune inflammation value has mostly been studied in malignant patients and is considered a prognostic biomarker.[20]

This study aims to examine the relationship between hemogram parameters, AD severity, total IgE, specific IgE, and skin prick tests in patients with AD.

METHODS

Ethics

The study was conducted with the permission of the Scientific Researches Evaluation and Ethics Committee of Ümraniye Training and Research Hospital (Date: 03.12.2024, Decision No: 327). All procedures were carried out in accordance with ethical rules and the principles of the Declaration of Helsinki.

AD diagnosis was based on the Hanifin-Rajka criteria, and severity was determined using clinical and treatment.[21]

Study Design and Sample

A total of 346 patients have been included in the study. This is a retrospective, cross-sectional study. Data from pediatric patients diagnosed with AD who presented to the Pediatric Allergy and Immunology outpatient clinic at Ümraniye Training and Research Hospital between January 1, 2024 and August 15, 2024, were retrospectively reviewed.

Patients with primary immune deficiencies, autoimmune diseases, chronic inflammatory conditions such as Crohn's disease, rheumatoid arthritis, or systemic lupus erythematosus, malignancies, and those using systemic corticosteroids or immunosuppressants in the past six months were excluded.

Measurements

Sociodemographic characteristics (age, gender), hemogram parameters (neutrophils, eosinophils, lymphocytes, platelets), total IgE levels, allergy history, and allergy test results were evaluated. Hemogram values such as NLR, PLR, SII, SIRI, neutrophil/lymphocyte/platelet ratio (NLPR), and PIV were calculated. Allergen-specific IgE levels were measured using the ImmunoCAP method, and skin prick tests were conducted for food and inhalant allergens. A specific IgE level of 0.35 kU/L or higher was classified as positive. The skin prick test was performed on patients using food allergens (milk, egg, hazelnut, peanut, walnut, pistachio) and inhalant allergens [house dust mites (Dermatophagoides), cat, pollen]. A test result showing an induration of 3 mm or more, in the absence of induration or dermatographism in the negative control, was considered positive. Those with positive skin prick tests and/or allergen-specific IgE were considered sensitized to the allergen.

Assessment of Atopic Dermatitis Severity

The severity of AD was determined according to clinical and treatment parameters. Patients using low-potency topical corticosteroids were classified as having mild AD, while those using medium-to-high-potency topical corticosteroids were classified as having moderate-to-severe AD.

Statistical Analysis

Data were analyzed using IBM SPSS version 29 software. Descriptive data were presented as number (n), percentage (%), median, and minimum-maximum values. Fisher's exact test or chi-square test was used for categorical variables, and Mann-Whitney U test for continuous variables. Significance level was set at $p<0.05$.

RESULTS

In this study, a total of 346 patients with AD were evaluated for their demographic, clinical, and laboratory characteristics. Among the patients, 53.8% (n=186) were male. The median age was 32.5 months (min: 1.0, max: 207.0) (**Table 1**).

Table 1. Demographic characteristics and severity of atopic dermatitis

Age (years), median (min-max)		32.5 (1.0-207.0)
Gender, n (%)	Female	160 (46.2)
	Male	186 (53.8)
Severity of atopic dermatitis	Mild	161 (46.5)
	Moderate-severe	185 (53.5)

Min: Minimum, Max: Maximum

The frequency of allergen sensitivity was evaluated according to the severity of AD. Sensitivities to house dust mite, cat dander, egg, and nuts were more prevalent in moderate to severe AD patients. However, there was no statistically significant difference in allergen sensitivity frequencies based on the severity of AD (**Table 2**).

Table 2. Allergen sensitivity frequencies according to atopic dermatitis severity

	Atopic dermatitis severity				
	Mild (n=161)		Moderate-severe (n=185)		p
	n	%	n	%	
House dust	29	18.0	39	21.1	0.474
Cat	14	8.7	18	9.7	0.741
Pollen	7	4.3	8	4.3	0.991
Milk	12	7.5	11	5.9	0.574
Egg	22	13.7	33	17.8	0.219
Nuts	2	1.2	4	2.2	0.689

When comparing laboratory parameters of mild and moderate-severe AD patients, the eosinophil count was significantly higher in moderate and severe AD patients compared to mild AD patients (330.0 [0-2860] vs. 260.0 [10-2780]; p=0.008). The eosinophil-lymphocyte ratio (ELR) was also significantly higher in moderate and severe AD patients (0.08 [0-1.01] vs. 0.06 [0-1.01]; p=0.004). No significant differences were found in other hemogram parameters, SII, SIRI, NLPR, and PIV between the groups (p>0.05) (Table 3).

Table 3. Comparison of laboratory parameters according to atopic dermatitis severity

	AD severity		
	Mild (n=161)	Moderate-severe (n=185)	p
	Median (min-max)	Median (min-max)	
WBC	8520.0 (3540-20530)	8660.0 (4410-18280)	0.241
NEU	2970.0 (730-10530)	3170.0 (550-16680)	0.054
BASO	40.0 (10-150)	40.0 (10-140)	0.322
EOS	260.0 (10-2780	330.0 (0-2860	0.008
EOS (%)	3.3 (0.1-20.0)	3.9 (0-21.0)	0.085
LYM	4090 (1610-15410)	4130 (1520-12270)	0.681
MONO	560 (66-1280)	530 (40-1690)	0.263
PLT	346 (33-773)	348 (38-623)	0.855
Total IgE	43.0 (1.0-7892.0)	63.0 (0-7503.0)	0.323
NLR	0.70 (0.12-5.72)	0.85 (0.09-9.22)	0.105
PLR	83.33 (8.81-230.56)	86.23 (6.52-242.74)	0.748
ELR	0.06 (0-1.01)	0.08 (0-1.0)	0.004
SII	218.99 (22.97-1831.3)	275.58 (9.39-2654.06)	0.102
PIV	134.33 (1.61-952.28)	136.87 (6.38-1259.92)	0.409
SIRI	0.41 (0.03-2.98)	0.43 (0.03-2.72)	0.279
NLPR	0.21 (0.03-3.36)	0.25 (0.02-5.03)	0.124

AD: Atopic dermatitis, Min: Minimum, Max: Maximum, WBC: White blood cell, NEU: Neutrophils, BASO: Basophil, EOS: Eosinophil, LYM: Lymphocyte, MONO: Monocyte, PLT: Platelets, IgE: Immunoglobulin E, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, ELR: Eosinophil/lymphocyte ratio, SII: Systemic immune-inflammation index, PIV: Pan-immune-inflammation value, SIRI: Systemic inflammatory response index, NLPR: Neutrophil-lymphocyte-platelet ratio

In the study, 137 patients had allergen sensitivity. When comparing laboratory parameters between AD patients with and without allergen sensitivity, WBC, basophils, eosinophils, and total IgE values were significantly higher in patients with allergen sensitivity (p<0.05). The ELR was also significantly higher in patients with allergen sensitivity (p<0.001). No significant differences were found in other hemogram parameters and inflammatory indicators (p>0.05) (Table 4).

Table 4. Comparison of laboratory parameters based on allergen sensitivity

	Allergen sensitivity		
	None (n=209)	Present (n=137)	p
	Median (min-max)	Median (min-max)	
WBC	8390.0 (3540-20530)	9210.0 (4410-19430)	0.021
NEU	3000.0 (550-16680)	3180.0 (730-8840)	0.561
BASO	40.0 (10-120)	40.0 (10-150)	0.005
EOS	260.0 (10-2860)	450.0 (60-2030)	<0.001
EOS (%)	2.9 (0-21.0)	4.6 (0.3-16.8)	<0.001
LYM	3940.0 (1610-15410)	4170.0 (1520-13300)	0.052
MONO	550.0 (40-1690)	550.0 (70-1570)	0.685
PLT	341.0 (35-642)	359.0 (33-773)	0.118
Total IgE	33.00 (0.0-7892.0)	142.5 (0-7503.0)	<0.001
NLR	0.81 (0.09-9.22)	0.82 (0.12-3.47)	0.538
PLR	85.98 (7.75-242.74)	83.85 (6.52-235.53)	0.478
ELR	0.06 (0-1.01)	0.1 (0.01-0.6)	<0.001
SII	251.25 (21.47-2654.06)	266.73 (9.39-1522.43)	0.993
PIV	136.87 (6.48-1259.92)	134.38 (1.61-1090.26)	0.771
SIRI	0.41 (0.03-2.98)	0.42 (0.03-2.50)	0.821
NLPR	0.24 (0.02-5.03)	0.23 (0.03-2.06)	0.550

Min: Minimum, Max: Maximum, WBC: White blood cell, NEU: Neutrophils, BASO: Basophil, EOS: Eosinophil, LYM: Lymphocyte, MONO: Monocyte, PLT: Platelets, IgE: Immunoglobulin E, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, ELR: Eosinophil/lymphocyte ratio, SII: Systemic immune-inflammation index, PIV: Pan-immune-inflammation value, SIRI: Systemic inflammatory response index, NLPR: Neutrophil-lymphocyte-platelet ratio

DISCUSSION

This study aimed to investigate the association between clinical and laboratory parameters in patients with AD based on the severity of the condition and allergen sensitivity. The significant findings indicate that moderate to severe AD patients exhibited higher eosinophil counts and ELRs compared to those with mild AD. In one study, there was no significant relationship between patients' peripheral eosinophil counts and disease severity.[22] Another study also could not detect a difference in peripheral blood eosinophil counts and percentages based on AD severity.[23] However, another study found that the severity of AD was proportional to the eosinophil/lymphocyte ratio.[24] In our study, eosinophil count and ELR ratio may provide predictive data related to the severity of AD disease. In a study conducted in our country, although no difference was found between the patient and control groups, the neutrophil-to-lymphocyte ratio was found to be significantly higher in patients with severe AD.[25] Another study suggested that the NLR could be used as a new marker.[26] In our study, no difference was found in the neutrophil/lymphocyte count and percentage in the blood according to the severity of AD. First of all, AD shows a complex pathogenesis, and many factors contribute to the severity of this disease. Although the NLR is a parameter that reflects the general inflammatory state, it may vary in different phases (acute, chronic) of AD and in each patient. NLR and PLR are considered indicators of systemic inflammation, yet in our study, these parameters did not show an association with AD severity, which may be attributed to several factors. First, AD is typically a localized inflammatory condition, and markers such as NLR and PLR, which reflect systemic inflammation, may not accurately capture the localized inflammation characteristic of AD. Additionally, the patients included in our study may have been in the mild or moderate stages of AD, where systemic inflammation is less pronounced. Finally, the association of NLR and PLR with this condition could be complex, and the clinical significance of these parameters may be better understood through further studies involving larger patient groups. More comprehensive studies are needed, especially those considering factors such as disease stages, individual differences in the inflammatory response, and genetic factors.

When comparing the laboratory parameters of patients with mild AD and moderate-to-severe AD, no significant difference was detected between the groups in terms of SII, SIRI, NLPR, and PIV. In a study conducted with febrile seizure patients, SII, SIRI, PIV, and NLPR values were found to be significantly higher in the FS group compared to the healthy control group.[27] In our study, the fact that inflammatory parameters such as SII, SIRI, NLPR, and PIV did not show a significant

difference between patients with mild and moderate-to-severe AD suggests that the inflammatory processes are not directly related to the severity of the disease. We believe that the localized inflammatory nature of AD and the fact that the patients evaluated were not in the severe stage of the disease contributed to these findings. These markers are generally more sensitive to systemic inflammation and may not accurately reflect the more localized inflammation associated with AD. It also suggests that these parameters may have limited value in reflecting the severity of AD or may be insufficient to represent the clinical characteristics of AD patients. More research is needed to clarify the potential roles of such parameters in determining AD severity.

House dust mite, cat, egg, and nut sensitivities were observed at higher rates in patients with moderate-to-severe AD. This is related to the immune system's overreaction to such allergens. In AD patients, the disruption of the skin barrier allows allergens to penetrate more easily, causing an exaggerated immune response. This is especially evident when exposed to common allergens such as house dust mites and animal dander. These findings suggest that severe AD patients tend to develop sensitivities to multiple allergens. In one study, the severity of AD was not associated with the presence of food sensitivity.[23] This contradiction highlights the complex nature of AD, which does not solely develop based on allergen sensitivity. The severity of AD may result from the combined effects of genetic, environmental factors, and immune system regulation.

When comparing the laboratory parameters of AD patients with and without allergen sensitivity, WBC, basophil, eosinophil, and total IgE values were significantly higher in patients with allergen sensitivity ($p<0.05$). The ELR was also significantly higher in patients with allergen sensitivity ($p<0.001$). No significant difference was observed in terms of NLR, PLR, and other hemogram parameters and inflammatory markers ($p>0.05$). In a study from Turkiye, while no significant differences were found in WBC, basophil, or NLR, the ELR and PLR were higher in patients with allergen sensitivity, although not statistically significant. However, total IgE was found to be significantly higher in patients with allergen sensitivity ($p<0.001$). Eosinophil, total IgE, and lymphocyte values were significantly higher in patients compared to the control group.[28] The differences between the two studies suggest that laboratory parameters alone may not be sufficient to determine allergen sensitivity in AD patients, and a multifaceted evaluation is required. It can be concluded that parameters such as eosinophil, ELR, and total IgE may be more reliable indicators of allergen sensitivity, whereas further studies are needed for other parameters.

Limitations

The severity of AD was determined based on clinical and treatment parameters. Due to the irregular maintenance of retrospective SCORAD records, an observational prospective study based on consistent records could yield better results. Also our study has a retrospective design, which has some limitations. In particular, the use of clinical records may introduce biases in the data collection process. Additionally, the retrospective approach may not fully reflect the variability encountered in clinical practice or the details of patients' treatment processes. Therefore, prospective studies are needed to enhance the accuracy of our findings.

CONCLUSION

Evaluating hematological parameters may assist in the clinical management of patients with AD. The ease of assessing hemogram parameters in many centers is extremely important for physicians working in this field. The routine measurement of eosinophil and total IgE levels, in particular, can provide a practical approach in determining the severity of AD and detecting allergen sensitivity. The findings of our study suggest that eosinophil count and total IgE levels are associated with AD severity and allergen sensitization. These parameters may be clinically useful in the management of AD. Specifically, patients with high eosinophil counts and total IgE levels may have a more severe disease course, which could guide treatment strategies. For example, elevated IgE levels and eosinophil counts may indicate the need for immunomodulatory therapies or biologic treatments. Additionally, these parameters can be used to monitor treatment response. Routine measurements could provide a practical approach for individualizing treatment plans and optimizing patient management. Future studies in this area will help us better understand the clinical significance of other laboratory parameters and inflammatory markers.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Scientific Researches Evaluation and Ethics Committee of Ümraniye Training and Research Hospital (Date: 03.12.2024, Decision No: 327).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

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Investigation of serum prostate-specific antigen levels in pregnant women with gestational diabetes mellitus; a cross-sectional, case-control study

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ABSTRACT

Aims: While many studies are showing that low serum prostate-specific antigen (PSA) levels are associated with the development of diabetes in male subjects, serum PSA levels in women with diabetes have not yet been investigated. Based on this information, we aimed to investigate serum PSA levels in pregnant women diagnosed with gestational diabetes mellitus (GDM).

Methods: This cross-sectional, case-control study was conducted with 88 pregnant women aged between 18 and 39 who applied to Ümraniye Training and Research Hospital, Department of Obstetrics and Gynecology, İstanbul, Turkiye, between May 2023 and September 2023. While the GDM group consisted of 44 pregnant women diagnosed with GDM between the 24th and 28th weeks of pregnancy, the control group consisted of 44 healthy pregnant women with normal 75-g oral glucose tolerance test (OGTT) results. Both groups were compared in terms of serum PSA levels.

Results: GDM and control groups were similar in terms of demographic features (p>0.005). The gestational week and BMI at blood sampling for serum PSA level were similar in the two groups (p=0.801, p=0.383, respectively). The median serum PSA level was found to be 1.22 ng/ml in the GDM group, while it was determined as 1.36 ng/ml in the control group (p=0.155).

Conclusion: The serum PSA level was lower in the GDM group than in the non-GDM group, yet this difference was not significant. Although the number of participants is too small to draw a definitive conclusion, serum PSA does not appear to be involved in the pathophysiology of GDM.

Keywords: Diabetes mellitus, gestational diabetes mellitus, pregnancy, prostate-specific antigen

INTRODUCTION

Synthesized primarily by the prostate gland's epithelial cells, prostate-specific antigen (PSA) acts to liquefy the seminal coagulum by degrading fibronectin and seminogelin, which allows the motile spermatozoa to be released.[1] PSA, which is thought to be specific to the prostate gland, has been used extensively over the years for the diagnosis and follow-up of both benign and malignant prostate diseases.[2] The use of highly sensitive immunoassays has shown that PSA is expressed in tissues beyond the prostate, and importantly, it is now detectable and measurable in females. Apart from the prostate gland, PSA is also expressed in normal lung tissue and lung tumors, primary and metastatic melanomas, pituitary tissue, and adenocarcinoma of the colon. In women, it has been shown that PSA is expressed in the endometrium, normal breast tissue, benign breast diseases, breast cysts, breast fluid, breast cancer, amniotic fluid during pregnancy, and breast milk.[3]

Diamandis et al.[4] were the first to discover that PSA levels in female serum are significantly lower, about 1000 times less, compared to those in male serum. According to reports, the normal range for PSA in women is ≤0.01 µg/L.[3] Following the discovery that PSA is present in breast tissue and detectable in serum, numerous studies have been conducted on its utility in diagnosing and monitoring both benign and malignant breast conditions in women.[5,6] Also, studies have shown that serum PSA levels vary throughout the menstrual cycle.[7,8] Interestingly, the literature has accumulated sufficient studies to allow for a meta-analysis on the effectiveness of PSA in diagnosing polycystic ovary syndrome (PCOS).[9]

Studies conducted over the years have shown that there is an inverse relationship between prostate cancer and diabetes mellitus (DM) in male subjects.[10,11] Although this inverse relationship is not clearly explained, different hypotheses have

been proposed. While some researchers suggest that chronic diabetes might lower testosterone levels, others argue that the vascular damage diabetes causes in the prostate may have a protective effect by restricting tumor growth.[12,13] The only thing clearly shown among these hypotheses is that lower serum PSA levels are detected in individuals with DM than those without DM.[14] Additionally, research indicates that the duration of diabetes adversely affects the serum PSA level in patients.[15,16] It is unclear why PSA is lower in male individuals with DM than in individuals without DM. It is suggested that high body-mass index (BMI), low testosterone levels in DM, impaired kidney functions due to DM, or medications used such as metformin may be responsible for low serum PSA levels.

Despite this apparent relationship between DM and PSA in male subjects, there is no data in the literature about serum PSA levels in female individuals with DM or pregnant women with gestational diabetes mellitus (GDM). Given this, our goal was to examine serum PSA levels in pregnant women diagnosed with GDM, hypothesizing that these levels would be lower in women with GDM compared to those without GDM.

METHODS

Approval for the study was granted by the Local Ethics Committee at İstanbul Ümraniye Training and Research Hospital (Date: 25.04.2023, Decision No: B.10.1.TKH.4.34.H.GP.0.01/137). The study followed the guidelines set out in the Declaration of Helsinki. All participants provided informed and written consent.

This cross-sectional, case-control study involved 88 pregnant women aged 18 to 39 years who applied to the Department of Obstetrics and Gynecology at Ümraniye Training and Research Hospital in İstanbul, Turkiye, from May 2023 to September 2023. The GDM group included 44 pregnant women diagnosed with GDM between the 24th and 28th weeks, whereas the control group comprised 44 pregnant women with normal results on a 75-g oral glucose tolerance test (OGTT). To control for potential confounding factors, the control group was matched with the GDM group in terms of age, BMI, gestational age, and gender of the fetus.

Participants with any pregestational diseases or a history of GDM in previous pregnancies were excluded from the study. Additionally, individuals who were smokers, had multiple pregnancies, or conceived through in vitro fertilization were also not included in the study. Those who developed any pregnancy-related disease were not included in the study. Those with PCOS or those without PCOS but with clinical findings of hyperandrogenism were not included in the study. Those with existing or previous benign or malignant breast disease or a history of breast surgery were not included in the study.

All participants underwent a 75-g OGTT between 24 and 28 weeks of gestation. The OGTT results were assessed based on the criteria set by the International Association of Diabetes and Pregnancy Study Groups. GDM was diagnosed if one of the following threshold values was met or exceeded: fasting glucose ≥92 mg/dl, 1-hour glucose ≥180 mg/dl, or 2-hour glucose ≥153 mg/dl.[17]

Age, BMI, obstetric history, laboratory and ultrasound findings, and perinatal outcomes for each participant were recorded.

Peripheral venous blood samples were taken from the participants in the morning hours after a minimum of 8 hours of fasting to analyze serum PSA levels within a week after the OGTT was performed. The blood samples collected were processed in accordance with the manufacturer's instructions for the PSA commercial kit used in the study. After standing at room temperature for 20 minutes, the samples were centrifuged at 2000 rpm for 20 minutes. The serum, collected from the upper part of the biochemistry tube post-centrifugation, was transferred to an Eppendorf tube and kept at -80°C. The Human Prostate Specific Antigen ELISA Kit (Sunredbio, Shanghai, China, Catalog No: 201-12-1714) was used to study serum PSA levels using the enzyme-linked immunosorbent assay technique. The kit provided a measurement range from 0.05 ng/ml to 10 ng/ml and had a sensitivity of 0.041 ng/ml. Inter- and intra-assay coefficients of variability of the kit were <12% and <10%, respectively.

Power analysis was performed using the G*power (v3.1.9.2) program to determine the sample size. The power of the study is expressed as 1-β (β=type II error probability). Based on the study conducted by Chen et al.[18], the effect size was calculated as d=1.575 as a result of the calculation made according to the difference in PSA measurements in the diabetes groups. It was calculated that there should be at least 22 participants in each group, 44 participants, to obtain 99% power at the α=0.01 level. Considering the possible dropouts during the study, 44 participants were included in each group. Since there was no dropout at the end of the study, the study was designed with 88 participants (44 in the GDM group and 44 in the control group).

Statistical Analysis

The data analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 25.0. The Kolmogorov-Smirnov test was used to assess the normality of the data distribution. Descriptive statistics were used to summarize the study data, including mean, standard deviation, median, minimum, maximum, frequency, and ratio. An independent t-test was used to compare two groups with parametric distributions, while the Mann-Whitney U test was used for non-parametric distributions. One-way ANOVA was used for comparing more than two groups with parametric distributions, and the Kruskal-Wallis test was used for non-parametric distributions. Correlation analysis was performed to explore relationships between quantitative variables, and the Chi-square test was used for categorical data. A p-value of less than 0.05 was considered statistically significant for all tests.

RESULTS

This study evaluated and compared the serum PSA levels between 44 pregnant women with GDM and 44 without GDM. There were no significant differences between the groups regarding age, pre-pregnancy BMI, total weight gain during pregnancy, BMI at delivery, gravida, and parity ($p>0.05$ for all). The GDM group had significantly higher fasting, 1-hour, and 2-hour glucose levels on the OGTT and higher HbA1c levels than the control group ($p<0.001$ for all). There were no significant differences in gestational age at delivery, delivery mode, newborn gender, or birth weight between the groups ($p>0.05$ for all). The GDM group had a significantly

lower 1st-minute Apgar score compared to the control group; however, the 5th-minute Apgar score, rates of NICU admission, incidence of neonatal hypoglycemia, and cases of neonatal hyperbilirubinemia were similar across both groups (p=0.008, p=0.057, p=0.496, p=0.120, p=0.093, respectively) (**Table 1**).

There were no significant differences in gestational age and BMI at the time of blood sampling for serum PSA levels between the two groups (p=0.801 and p=0.383, respectively). The median serum PSA level was 1.22 ng/ml in the GDM group compared to 1.36 ng/ml in the control group, with a p-value of 0.155 (**Table 2**).

Table 2. Comparison of GDM and control groups in terms of serum PSA levels

	Control group (n=44)	GDM group (n=44)	
	Mean±SD median (min-max)	Mean±SD median (min-max)	p
Gestational week at blood sampling	26.3±1.1 26 (24-28)	26.3±1.4 27 (24-28)	0.801
BMI at blood sampling (kg/m²)	25.1±3.2 24.9 (19.4–29.7)	25.7±2.3 25.3 (22–29.9)	0.383
Serum PSA (ng/ml)	2.28±1.81 1.36 (0.96–6.99)	2.49±2.59 1.22 (0.67–10)	0.155

Mann-Whitney U test, GDM: Gestational diabetes mellitus, PSA: Prostate-specific antigen, BMI: Body-mass index, Min: Minimum, Max: Maximum, SD: Standard deviation

DISCUSSION

The study focused on serum PSA levels in pregnant women with and without GDM. In line with our initial hypothesis, we observed a lower median serum PSA level in the GDM group compared to the non-GDM group, but this difference was not statistically significant.

Waters et al.[19] investigated the association between diabetes and prostate cancer risk in a multi-ethnic cohort. They found that the mean PSA levels were significantly lower in individuals with diabetes than those without diabetes (1.07 ng/ml and 1.28 ng/ml, respectively; p=0.003).[19] In 2009, Müller et al.[20] published a study investigating the relationship between diabetes, BMI, and serum PSA levels. The study involved 778 men aged 50 to 74 randomly selected from a large population-based cohort study conducted in Germany between 2000 and 2002. While the median serum PSA level was 1.0 ng/ml in diabetic men, it was 1.3 ng/ml in non-diabetic men. Also, there was a significant decrease in mean PSA levels in individuals with high (6.1-6.9%) and very high (7%) HbA1c compared to individuals with normal HbA1c values (16% and 30%, respectively).[20]

In 2017, Al-Asadi et al.[16] published a study comparing 70 diabetic and 70 non-diabetic subjects in terms of serum PSA levels. The study found that the mean serum PSA level was significantly lower in diabetic men than in non-diabetic men (1.97 ng/ml and 2.60 ng/ml, respectively, p=0.001). Additionally, age was significantly associated with PSA levels in non-diabetic men. Still, no such relationship was observed in diabetic men.[16] In a paper published by Kobayashi et al.[21] in 2020, among 14486 male individuals who applied to the hospital for routine health screening, median serum PSA levels were found to be significantly lower in 1403 patients with DM compared to 13083 individuals without DM (0.77 ng/ml and 0.81 ng/ml, respectively; p=0.005). After adjusting age,

Table 1. Comparison of GDM and control groups in terms of demographic characteristics, laboratory findings, and perinatal outcomes

		Control group (n=44)	GDM group (n=44)	
		Mean±SD median (min-max) n (%)	Mean±SD median (min-max) n (%)	p
Age (years)		29.14±4.75	30.09±6.09	0.414[m]
Pre-pregnancy BMI (kg/m²)		23.3 (18.2–29.3)	23.7 (20–29.5)	0.488[n]
Weight gained throughout pregnancy (kg)		12.5±5.2	13.5±5.3	0.357[m]
BMI at delivery (kg/m²)		28.4±3.2	29.3±3.3	0.229[m]
Gravida		2.3±1.6	2.3 ±1.5	1.00[m]
Parity	Multiparous	23 (52.3)	29 (65.9)	0.193[p]
	Nulliparous	21 (47.7)	15 (34.1)	
75 g OGTT fasting blood glucose level (mg/dl)		83.5 (70–92)	92 (73–138)	<0.001[n]
75 gr OGTT 1st-hour blood glucose level (mg/dl)		129.2±24.5	180±40	<0.001[m]
75 g OGTT 2nd-hour blood glucose level (mg/dl)		102±18.1	144.8±35.7	<0.001[m]
HbA1c (%)		4.8±0.2	5.2±0.5	<0.001[m]
Gestational age at delivery (weeks)		39±1.7	38.3±2.2	0.340[m]
Mode of delivery	Vaginal birth	20 (45.5)	20 (45.5)	1.00[p]
	Cesarean section	24 (54.5)	20 (45.5)	
Gender of the newborn	Female	16 (36.4)	24 (54.5)	0.087[p]
	Male	28 (63.6)	20 (45.5)	
Birth weight (g)		3191±462.9	3353±521.4	0.128[m]
1st minute Apgar score		8 (5-9)	7 (5-9)	0.008[n]
5th minute Apgar score		9 (7-10)	9 (4-10)	0.057[n]
NICU admission		13 (29.5)	16 (36.4)	0.496[p]
Neonatal hypoglycemia		4 (6.8)	9 (20.5)	0.120[p]
Neonatal hyperbilirubinemia		2 (4.5)	8 (18.2)	0.093[p]

[m] Independent-T test; [n] Mann-Whitney U test; [p] Chi-square test, GDM: Gestational diabetes mellitus, BMI: Body-mass index, OGTT: Oral glucose tolerance test, HbA1c: Hemoglobin A1c, NICU: Neonatal intensive care unit, Min: Minimum, Max: Maximum, SD: Standard deviation

significant decreases in PSA were found, especially in diabetic men taking antidiabetic drugs. Also, it was observed that PSA levels were significantly reduced in diabetic men with higher HbA1c and fasting blood glucose levels.[21]

Unlike the previous studies, other research has indicated that serum PSA levels may be lower in individuals with diabetes than those without, though this difference lacks statistical significance. One such study, conducted by Naito et al.[22], involved 195 diabetic men and 1.977 non-diabetic men. The study reported that the mean serum PSA level was lower in the diabetic group than in the non-diabetic group. However, this difference was insignificant (p=0.286). After adjusting for age and age+BMI, the mean PSA level in the diabetic group was still lower than that in the nondiabetic group, although not statistically significant.[22] Ainahi et al.[23] conducted a study published in 2018 examining 470 diabetic men and 869 non-diabetic men between January 2015 and April 2016. The results showed no significant difference in mean PSA levels between the two groups (1.31±0.04 ng/ml for diabetics vs. 1.36±0.03 ng/ml for non-diabetics; p=0.380). The study also indicated mean serum PSA levels increased with age in diabetic and non-diabetic men.[23]

A meta-analysis published in 2021 reviewed the relationship between serum PSA levels and diabetes, incorporating data from 8 studies. The analysis reported that diabetic patients generally had significantly lower PSA levels compared to non-diabetic individuals. The authors concluded that the observed lower PSA levels in diabetics are more likely related to the duration and severity of the disease or the use of anti-diabetic medications rather than the diabetes diagnosis itself.[14]

Similar to the studies referenced earlier, our findings indicated that the median serum PSA level was lower in the GDM group than in the non-GDM group, but this difference did not achieve statistical significance. Furthermore, we could not establish a significant relationship between serum PSA levels and GDM-related factors, including HbA1c and BMI.

All existing studies on the relationship between serum PSA and diabetes have focused on male subjects, consistently finding lower PSA levels in individuals with diabetes compared to those without. Factors such as age, BMI, duration and severity of diabetes, and treatments used have been shown to influence serum PSA levels in diabetic men. However, no research has yet investigated serum PSA levels in diabetic women. This study is pioneering in assessing serum PSA levels in pregnant women with GDM, and we anticipate it will provide a basis for future studies exploring PSA's role in GDM's pathophysiology.

Limitations

This study has notable limitations, including the small sample size and that serum PSA levels were measured only once. Additionally, the lack of data on how serum PSA levels change throughout normal pregnancy and the absence of follow-up on PSA levels after blood glucose regulation in women with GDM are significant constraints.

CONCLUSION

Our results indicated that the median serum PSA level was lower in the GDM group than in the non-GDM group; however, this difference was not statistically significant. We could not determine a significant PSA cutoff value for GDM diagnosis, but our study suggests that GDM negatively influences serum PSA levels in a currently unexplained way.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval for the study was granted by the Local Ethics Committee at İstanbul Ümraniye Training and Research Hospital (Date: 25.04.2023, Decision No: B.10.1.TKH.4.34.H.GP.0.01/137).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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The impact of vitamin D supplementation on reproductive outcomes in women with polycystic ovary syndrome: a randomized controlled study

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ABSTRACT

Aims: This study aims to evaluate the effectiveness of vitamin D supplementation treatment on reproductive outcomes in women with polycystic ovary syndrome (PCOS).

Methods: The study involved 235 women aged 20-40 with PCOS who were seeking treatment at Private infertility Clinic in Turkiye. The participants were divided into two groups: 123 in the control group and 115 in the intervention group, chosen at random. Their age, body-mass index (BMI), education level, employment status, and PCOS symptoms were assessed. Statistical significance between the case and control groups was compared using the chi-squared and Fisher's exact tests.

Results: There were no significant differences in age, BMI, education level, employment status, and PCOS symptoms such as menstrual irregularity, amenorrhea, hirsutism, hair loss and acne between the intervention and control groups (p-value>0.05). There were significant differences in clinical pregnancy rates (CPR) between the intervention and control groups (p-value<0.05). The two groups showed no significant differences in live birth rates and clinical miscarriage rates (p-value>0.05).

Conclusion: Based on the findings, it has been revealed that supplementing with vitamin D has a positive impact on CPR. Vitamin D supplementation may support the improvement of fertility in women with PCOS, although the exact mechanisms and effectiveness are still under study.

Keywords: PCOS, vitamin D supplementation, pregnancy rates, reproductive outcomes

INTRODUCTION

The most common endocrine disorder in females at the age of childbearing is considered to be polycystic ovary syndrome (PCOS).[1] PCOS is highly prevalent among women as its prevalence is reported to be 9.2% worldwide (95% CI: 6.8–12.5%).[2] This disorder is the most relevant cause of hyperandrogenism, hirsutism and anovulatory infertility in the developed countries.[3,4] The most prevalent symptom of PCOS is suggested to be infertility, approximately 75% women diagnosed with PCOS suffer from infertility due to anovulation, which makes PCOS by far the most relevant cause of anovulatory infertility.[5] It is a heterogeneous androgen excess disorder with various severities of metabolic and reproductive dysfunctions.[6] Treatment of women who are diagnosed with PCOS is reliant on their symptoms. Current therapies available for infertility caused by PCOS generally involve ovulation induction, monitoring ovulation, assisted reproduction technologies and ovarian perforation. additionally, the use of some nutrients such as minerals, unsaturated fatty acids, vitamins, etc. has seen a fair amount of attention as an adjunction.[7]

Vitamin D ("serum concentrations of 25-hydroxycalciferol [25-(OH)D3]") plays a crucial role in regulating calcium and phosphate levels, essential for the health of muscles, bones, and teeth.[8] Additionally, it may help reduce the risk of diabetes, cancer, autoimmune disorders, and migraines.[9] Vitamin D insufficiency is the most common medical issue worldwide. According to studies, over 1 billion individuals worldwide suffer from Vitamin D deficiency, with nearly half of the world's population experiencing some level of insufficiency.[10] Compared to the general population, women with PCOS are more likely to be vitamin D deficient. Numerous studies suggest a connection between Vitamin D deficiency and the development and symptoms of PCOS.[11] Noticeably, 67-85% of individuals with PCOS also experience vitamin D

deficiency.[12,13] Additionally, this deficiency may play a role in the development of insulin resistance and metabolic syndrome associated with PCOS.[14]

Due to the role of vitamin D in ovulation dysfunction as well as the anti-inflammatory benefits of vitamin D, it is expected for vitamin D supplementation to have a positive effect in regulating the growth of follicles and therefore ovulation and ultimately fertility.[15] Recently, supplementation has drawn considerable attention for its potential benefits in preparing PCOS patients for pregnancy. Its protective effects against oxidative stress and its role in maintaining calcium ion levels may enhance fertilization, cleavage, implantation, and placental development. However, findings on the impact of vitamin D supplementation on pregnancy rates remain inconsistent. Some studies indicate that it can improve pregnancy rates in PCOS patients, while others show no significant effect.[16] Consequently, this study aims to evaluate the impact of vitamin D supplementation on reproductive outcomes in women with PCOS. The main goal of this study is to assess the effects of vitamin D in infertility of Turkish women diagnosed with PCOS.

METHODS

This randomized controlled study was conducted in 2023-2024 on 235 PCOS patients referred to Women's Clinics of Bezmialem Hospital. The study was conducted in accordance with the Declaration of Helsinki. Ethics Committee Approval The study was conducted with the permission of Bezmialem Vakıf University Ethics Committee (Date: 31.12.2024, Decision No: 2024/432).

Figure shows the flowchart of patient selection. Block method was used for randomization. First, blocks were created with the combination AAABBB and then all possible permutations were made for this combination. Finally, a number was assigned to each composition. This study was a single-blind study. The drug intervention in two groups was the same in terms of the shape, color or appearance of the drugs. The patients of both groups were unaware of the type of the group they were in, while the doctor and researcher were aware of the type of groups or therapeutic intervention.

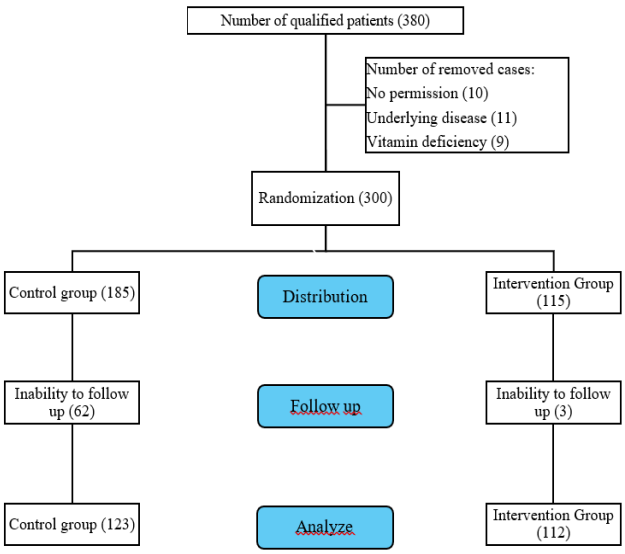

Figure. Women with polycystic ovary syndrome selection flowchart

The present study was a single-blind clinical trial study. Inclusion criteria included: women aged 20-40 with PCOS diagnosis, patients without celiac disease, patients without vitamin D deficiency, and those who consented to participate in the study.

Exclusion criteria included: patients with underlying disease, previous use of ovulation induction, previous use of metformin, patients who lacked consent, and those with vitamin D deficiency. The cut-off value<20 ng/ml was considered vitamin D deficiency. The sample size included 235 patients with PCOS. After collecting basic information including age, marital status, education, body-mass index (BMI), presence of PCOS symptoms such as acne, menstrual irregularity, amenorrhea, hirsutism and hair loss at the time of visit was checked and the patients with a serum level greater than or equal to 30 ng/ml of vitamin D (25-hydroxyvitamin D3) were included in the study and then they were divided into two groups based on the random number table. The other group was prescribed metformin 500 mg daily plus vitamin D 50 thousand units weekly (intervention group) orally for 36 weeks. Then the reproductive outcomes information of the two groups was compared in two groups.

The sample size was equal to 235 people by considering error=0.05 and 80% power and using the sample size formula. SPSS statistical software (version 22) was used to data analysis and descriptive statistics methods including frequency and percentage. Fisher's exact test and chi-squared test were used to test whether two categorical variables are related to each other. p value less than 0.05 was considered as significant.

RESULTS

The mean age of women with PCOS in the intervention group was 29.39±5.30 years, and their mean BMI upon entering the group was 27.01±3.23 kg/m^2. The mean age of PCOS patients in the control group was 30.41±6.02 years, and their mean BMI upon entering the group was 27.25±3.39 kg/m^2.

There were no significant differences in age between the intervention and control groups at the time of enrolment (p-value>0.05). No significant BMI differences existed between the intervention and control groups at enrollment (p-value>0.05). There were no significant differences in the rates of education level and job status between the intervention and control groups (p-value>0.05) (**Table 1**).

PCOS symptoms including menstrual irregularity, amenorrhea, hirsutism, hair loss and acne were not significantly different in both intervention and control groups (p-value>0.05). The clinical pregnancy rates (CPR), clinical miscarriage rates (CMR) and live birth rates (LBR) were compared between the two groups (**Table 2**).

As illustrated in **Table 2**, CPR was (39.3%), CMR (32.0%) and LBR was (90.0%) in women in the intervention group. CPR was (27.6%), CMR (35.3%), and LBR was (91.0%) in the control group. There were significant differences in CPR between the intervention and control groups (p-value<0.05). The two groups had no significant differences in live birth rate (p-value>0.05). There were no meaningful differences in CMR between the two groups (p-value>0.05).

Table 1. The patients' demographic characteristics between the two groups

		"Intervention mean±SD (min–max) n (%)" n=112	"Control mean±SD (min–max) n (%)" n=123	p-value
Female age (years)		29.39±5.30 (20–40)	30.41±6.02 (20-40)	.170*
BMI (kg/m²)		27.01±3.23 (20–38)	27.25±3.39 (20-37)	.573*
Education level	High school	47 (42.0)	56 (45.5)	.655*
	Bachelor	50 (44.6)	55 (44.7)	
	Master	15 (13.4)	12 (9.8)	
Job status	Employed	44 (39.3)	56 (45.5)	.582*
	Housewife	68 (60.7)	67 (54.5)	
Menstrual irregularity	No	22 (19.6)	27 (22.0)	.664*
	Yes	90 (80.4)	96 (78.0)	
Amenorrhea	No	111 (99.1)	121 (98.4)	.617**
	Yes	1 (0.9)	2 (1.6)	
Hirsutism	No	27 (24.1)	25 (20.3)	.531*
	Yes	85 (75.9)	98 (79.7)	
Hair loss	No	35 (31.3)	35 (28.5)	.640*
	Yes	77 (68.8)	88 (71.5)	
Acne	No	57 (50.9)	68 (55.3)	.500*
	Yes	55 (49.1)	55 (44.7)	

BMI: Body mass index, Min: Minimum, Max: Maximum, *Chi-squared test **Fisher's exact test

Table 2. The patients' outcomes between two groups

		Intervention n (%) n=112	Control n (%) n=123	p-value
CPR	No	68 (60.7)	89 (72.4)	.004*
	Yes	44 (39.3)	34 (27.6)	
CMR	No	30 (68.0)	22 (64.7)	.671*
	Yes	14 (32.0)	12 (35.3)	
LBR	No	3 (10.0)	2 (9.0)	1.000**
	Yes	27 (90.0)	20 (91.0)	

*Chi-squared test **Fisher's exact test. CPR: Clinical pregnancy rates, CMR: Clinical miscarriage rates, LBR: Live birth rates

DISCUSSION

The current randomized controlled trial study examined the impact of vitamin D supplementation on reproductive outcomes in women with PCOS. The findings indicate that the use of vitamin D supplementation significantly affects CPR in women with PCOS. However, vitamin D did not have a statistically significant effect on CMR and LBR. This section compares and discusses the current study's findings with previous studies' results. Limited research was done on the role of vitamin D supplementation in increasing the chance of getting pregnant in women with PCOS. Most performed investigations focus on the effect of vitamin D supplementation on "assisted reproductive technology" (ART) outcomes such as in vitro fertilization (IVF) in women with PCOS.[13,17-19]

Rashidi et al.[20] found that calcium-vitamin D plus metformin improving CPR in patients with PCOS. This study was to assess the impacts of calcium-vitamin D and metformin on regularity of menses, number of large follicles and pregnancy rates. Pal et al.[21] found that vitamin D is relevant for procreative success for getting pregnant in infertile PCOS patients. They showed that vitamin D status associates to reproductive outcome. Varbiro et al.[22] in a comprehensive review reported the positive effects of vitamin D supplementation on CPR in PCOS women. Nosseir et al.[23] showed that vitamin D supplementation improved pregnancy rates in infertile women with PCOS in a randomized, controlled clinical preliminary investigation. Zhuang et al.[24] reported that combined metformin, clomiphene, vitamin D could significantly improve endocrine conditions and clinical symptoms and enhance CPR and ovulation rates. Yang et al.[15] found that vitamin D supplementation donate to the higher ovulation and CPR. According to Khalifa et al.[25] women who have sufficient levels of 25(OH)D are significantly more likely to achieve clinical pregnancies compared to those deficient in 25(OH)D. According to Katyal et al.[26], inositol and vitamin D were shown to alleviate symptoms, boost fertility, enhance metabolic control, and reduce long-term health risks. Piao et al.[27] found that vitamin D supplementation can enhance pregnancy rates and alleviate fundamental hormonal disorders. The results of these studies are compatible with our findings. However, contradictory results have been reported in some studies.

Sulaiman et al.[28] conducted comprehensive research on the positive effects of vitamin D on the reproductive system of women. They found doubts and suspicions regarding the correlation between vitamin D intake and improved PCOS symptoms. The studies conducted across multiple laboratories did not yield definite findings. Firouzabadi et al.[29], compared two groups to examine pregnancy rates, PCOS symptoms, and menstrual regularity. Group 1 received daily metformin, while group 2 was treated with calcium, vitamin D, and metformin for a duration of six months. The study suggests that calcium and vitamin D supplementation may lead to improvements in weight reduction, follicular development, symptoms related to androgen access, and menstrual regularity in PCOS patients. Interestingly, the study found no significant difference in pregnancy rates between the two groups. Shojaeian et al.[30] in a systematic review and meta-analysis examined calcium and vitamin D supplementation effects on follicular responses, menstrual cycles, and metabolic factors in women with PCOS.

Studies have shown that prescribing calcium and vitamin D supplementation along with metformin improved follicular maturation, pregnancy rate had no significant difference in different groups after treatment with calcium and vitamin D supplementation. Regarding the effect of vitamin D supplementation on the CMR and LBR not many studies were found to compare the findings.

While a few limited studies have not found a link between vitamin D supplementation and increased CPR, the majority of previous research has demonstrated a direct impact of these supplements on CPR. As a result, it is advised that both patients and healthcare professionals be informed about these effects.

Limitations

This study has several limitations. One significant limitation is the sample size collected from single center. Thus, it is required to conduct further studies with larger sample sizes to understand better the effect of Vitamin D supplementation on reproductive outcomes in PCOS patients.

CONCLUSION

In conclusion, the present proof indicated that vitamin D supplementation may enhance the CPR of women with PCOS based on standard medicine, supplying a specific basis for the clinical usage of vitamin D supplementation in patients in the future. Nevertheless, more valuable studies are still required because of the heterogeneity and quality of the contained examinations.

As a consequence of our study with a randomized control group and a one-year follow-up period followed that the use of vitamin D supplementation in women with PCOS was statistically significant in increasing the CPR. There were no significant differences in LBR and CMR between the intervention and control groups. Future examinations are required to systematically evaluate these concepts because the public health, clinical, and financial implications of such a easy, secure, and cheap technique can be effective.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Bezmialem Vakıf University Ethics Committee study (Date: 31.12.2024, Decision No: 2024/432).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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What is the role of body-mass index, waist circumference and waist to height ratio in predicting the risk of high blood pressure in children aged 3-18 years?

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ABSTRACT

Aims: Obesity has increased among children in recent years, becoming one of the most serious health issues due to an increase in the risk of cardiovascular illnesses. The aim of this study was to assess prevalence of obese and hypertensive children aged 3-18 years and to determine the role of body-mass index (BMI), waist circumference (WC) and waist to height ratio (WHtR) in predicting the risk of high blood pressure (BP) and hypertension (HT).

Methods: The demographic characteristics, BMI, WC, WHtR, and BP percentiles were evaluated, and the relationship between high BP and BMI, WC and WHtR was investigated.

Results: The study included 752 children aged 3-18 years, 73.9% of children aged 3 to 12 years old. Obese children were found at 8.4%, overweight at 13%, HT at 9.6%, and high BP at 8%. The risky WHtR ratio (≥0.5) for abdominal obesity was found to be 23.7%. Males had significantly higher rates of obesity, risky WHtR, and HT ($p<0.05$). Being between 3 and 12 years of age, overweight, obese and risky WHtR were the most prevalent risk factors for high BP and HT ($p<0.05$).

Conclusion: Obesity and HT rate was increased, particularly in males. Since risky WHtR and increased BMI have been determined to be the most important risk factors for high BP and HT, it is critical to monitor BP more frequently, especially in the neglected 3-12 age group, in the presence of risky WHtR and higher BMI.

Keywords: Children, high blood pressure, hypertension, abdominal obesity, waist circumference, waist to height ratio

INTRODUCTION

Obesity is a condition characterized by abnormal fat accumulation due to energy balance disorders, first recognized by the World Health Organization (WHO) in 1948. It is caused by various genetic, physiological, behavioral, sociocultural, and environmental factors.[1] Childhood obesity can lead to various health issues, including diabetes, hypertension (HT), and psychosocial disorders. Due to limited pharmacotherapy options, it is recommended to implement a program involving nutrition, exercise, and behavioral changes, breastfeed exclusively for at least six months, reduce screen time, and increase physical activity to reduce obesity risk.[1]

WHO reported a significant increase in overweight and obese children and adolescents aged 5-19, from 4% in 1975 to 18% in 2016. Over 124 million children and 41 million children under 5 were found to be overweight or obese.[3] Recent studies indicate that around 20% of school-aged children in European countries are overweight or obese, highlighting the global health threat of obesity.[2]

Obesity can be determined using methods like skinfold thickness measurement and bioelectrical impedance, but these are costly and not easily accessible. BMI is a widely used and easy method for classifying obesity, calculated from height and weight in children. Z-scores (SDS) or percentiles are used to assess BMI in children, which vary based on age and gender.[1] The waist/height ratio (WHtR) can also be used to assess obesity in children. Studies have shown that a WHtR≥0.5 predicts kardiovascular diseases and diabetes in adults and children.[3]

HT is a condition characterized by high blood pressure (BP) on the vascular wall, influenced by lifestyle, behavioral, environmental, and genetic factors.[4] Risk factors include family history, obesity, race/ethnicity, physical inactivity, and high sodium intake.[4,5] Primary HT is common in children and adolescents, especially those over six years old, and may be linked to obesity. Secondary HT is more common in childhood, with kidney and renovascular diseases being the most common causes. Therefore, all children diagnosed with HTN in childhood should be evaluated for secondary causes.[5]

The prevalence of high BP and HT in children aged 1-12 years has increased in recent years, linked to an increase in obese children, according to the National Health and Nutrition Examination Survey data.[7] This increase has been associated with the increase in obese children. Normal and high BP values for children vary based on age, height, and gender.[4] Around 3.5% of United States (US) children have HT, while 2.2-3.5% have high BP. Central European countries have a prevalence of 2.2-4.9%, while Southern and Western European children have rates ranging from 9% to 13%.[6] Turkiye's childhood HT prevalence varies between 8.5% and 15%, with few studies on its epidemiology.[5]

Obese children have a higher prevalence of HT compared to lean children, with a 3 times higher prevalence in obese adolescents.[7] Primary HT prevalence in children is increasing due to the increasing epidemic of overweight and obesity. It is diagnosed in 4-14% of overweight children and 11-33% of obese children, indicating a significant concern as both overweight and HT are often transmitted from childhood to adulthood.[7]

BMI and waist circumference (WC) are commonly used to define obese children and adolescents, but BMI is not a measure of fat distribution and different cut-offs are used based on age and gender. WC indicates abdominal obesity, which is clinically useful as a predictor of metabolic syndrome, type 2 diabetes, dyslipidemia, HT, and coronary artery disease.[8] Studies show that cardiovascular death and myocardial infarction increase with WC.[8] The WHtR is superior to BMI or WC in predicting metabolic diseases like HT, type 2 diabetes, dyslipidemia, and metabolic syndrome in children.[9]

This study aims to assess the prevalence of obesity and HT in children aged 3-18 years and to determine the role of BMI, WC and WHtR in predicting the risk of high BP and HT in children.

METHODS

The Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee approved the study (Date: 12.09.2022, Decision No: 146/25). Informed consent were obtained from the children' parents. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study, a prospective cross-sectional study, involved 752 children aged 3-18 from Turgut Özal Family Health Center between 05.09.2022-05.09.2023.

Children with prior HT diagnoses due to renal, cardiovascular, medication, neurological, or other reasons and those with anatomical abnormalities in the areas to be measured were excluded children included in the study had anthropometric measurements, systolic blood pressure (SBP) and diastolic blood pressure (DBP) according to the specified criteria. Body weights were measured using a calibrated electronic scale with a sensitivity of (±) 100 g. The height measurements of the children were measured in centimeters on the vertical plane using a stadiometer. The BMI value was calculated by dividing the measured body weight by the square meter of the height. The calculated values were used for percentile and SDS calculations using the WHO data for the ages of 2-20. Weight classification in children and adolescents was made according to the WHO classification.[1,10] Children whose BMI values were calculated below the 5th percentile for age were classified as underweight, those between the 5th and 85th percentiles as normal weight, those between the 85th and 95th percentiles as overweight, and those above the 95th percentile as obese.[1,10]

Children's BP was measured using a calibrated air sphygmomanometer and a cuff appropriate for their age and arm circumference. SBP and DBP were measured, with resting time of at least 5 minutes before measurement. Percentile and SDS calculations were made according to the American Pediatric Academy (AAP) 2017 guideline.[4] For children under 13 years of age, <90th percentile is normal BP; ≥90th percentile - <95th percentile (120/80 mm Hg-<95th percentile) (whichever is lower) is high BP; ≥95th percentile - <95th percentile+12 mmHg (130/80 to 139/89 mm Hg) (whichever is lower) is Stage 1 HT, ≥95th percentile. Percentile+12 mm Hg (≥140/90 mm Hg) (whichever is lower) was evaluated as stage 2 HT. Children aged 13 and above have different blood pressure levels: normal (<120/<80 mm Hg), high (120/<80-129/<80 mm Hg), stage 1 HTN (130/80-139/89 mm Hg), and stage 2 HT (≥140/90 mm Hg).[4] If their BP exceeds the 90th percentile, they are measured twice, averaged, and staged for further evaluation.

WC was measured with a 1 mm precision tape measure, placed in the midline between the lower part of the lowest rib and the highest point of the iliac crest, while standing upright with feet together. WC SDS was calculated using WC percentiles in Turkish children and adolescents. The WHtR was calculated as the ratio of WC (cm) to height (m), and a cut-off value of 0.5 has been used as a threshold. Those with a WHtR of ≥0.5 were considered to be at risk for abdominal obesity.[11]

Statistical Analysis

Data analysis was performed with SPSS 27.0 program and was studied with 95% confidence level. Frequency (n) and percentage (%) for categorical (qualitative) variables mean (Average), standard deviation (SD), minimum and maximum statistics were given for numerical (quantitative) variables. Logistic regression, Chi-square, Pearson correlation test, One-way ANOVA tests were used in the study. Logistic regression was used in determining the factors affecting HT in the study, Chi-square was used in the relationships between grouped variables, one-way ANOVA was used in comparing the measurements according to the groups, and Pearson correlation test was used in the relationships between the measurements.

RESULTS

The study involved 752 children, with 54% male and 46% female, with an average age of 10.05±3.64. The majority were aged 3-12, with 73.9% aged 3-12 and 26.1% aged 13 and over. 2.4% had chronic diseases, with asthma (38.9%), diabetes

(16.7%), and epilepsy (16.7%) being the most common diagnoses.

When the BMI distribution of the children was examined, 67.3% were normal, 11.3% underweight, 13.0% overweight, and 8.4% obese. The majority of children did not have a risky WHtR for abdominal obesity (76.3%). 82.4% had normal BP, with high BP rates at 8.0% and HT at 9.6%. Demographic and clinical characteristics are provided in Table 1 and Table 2.

Table 1. Distribution of demographic and clinical characteristics of children

n=752		n (%)
Gender	Male	406 (54)
	Female	346 (46)
Age(years)	3-12	556 (73.9)
	≥13	196 (26.1)
Chronic disease	No	734 (97.6)
	Yes	18 (2.4)
Diagnosis	Acute rheumatic fever	1 (5.6)
	Astma	7 (38.9)
	Behçet's disease	1 (5.6)
	Celiac disease	1 (5.6)
	Type 1 diabete mellitus	3 (16.7)
	Epilepsy	3 (16.7)
	Familial Mediterranean fever	1 (5.6)
	Pituitary insufficiency	1 (5.6)
	Inflammatory bowel disease	1 (5.6)
WHtR	No risk	574 (76.3)
	Risky	178 (23.7)
BMI	Underweight	85 (11.3)
	Normal	506 (67.3)
	Overweight	98 (13)
	Obese	63 (8.4)
Blood pressure	Normal	620 (82.4)
	High	60 (8)
	Hypertension	72 (9.6)

WHtR: Weist to height ratio, BMI: Body-mass index

Age distribution between males and females were similar (73.9% and 74%), with a significant relationship between gender and BMI, risky WHtR, and BP levels (p<0.05). Males had higher obesity (11.6%), risky WHtR (28.1%), and HT (12.3%) rates, but no significant relationship was found with age and chronic disease (p>0.05) (Table 3).

A significant relationship found between children's age and BMI and BP levels (p<0.05), with obesity (8.5%) and HT (12.2%) more common in children aged 3-12 years compared to those aged 13 and over, but not for chronic disease and risky WHtR (p>0.05) (Table 3). A significant correlation found between children's BP, BMI, and risky WHtR (p<0.05), with obesity (33.3%) and WHtR (72.2%) more prevalent in children with HT, but not in chronic disease (p>0.05) (Table 3).

There was a significant relationship between BP levels and BMI levels and risky WHtR in males and females, with obesity and risky WHtR being higher in females and males with high-tension (HT) (p<0.05). The relationship was not significant for chronic disease (p>0.05). A significant correlation found between BP levels, BMI, and risky WHtR in children aged 3-12 and over 13 years (p<0.05), with higher risky WHtR and obesity in children with HT, but not in chronic disease and BMI (p>0.05) (Table 3).

Table 2. Descriptive statistics of children's androtopometric and blood pressure measurements

	Min-Max	Mean±SD
Age (years)	3.29-18.01	10.05±3.64
Weight	11.75-107.15	37.15±17.59
Weight percentile	0.03-99.99	54.76±30.33
Weight SDS	-3.4-3.63	0.18±1.1
Height	90-192	140.19±21.11
Height percentile	0.25-99.99	60.46±27.52
Height SDS	-2.81-4.3	0.37±1
BMI	11.86-34.59	17.78±3.8
BMI percentile	0.02-99.98	48.97±32.88
BMI SDS	-3.74-3.58	-0.09±1.26
WC	45-110	64.09±11.34
WC SDS	-3.28-4.31	0.73±1.13
WHtR	0.33-0.67	0.46±0.05
SBP	70-140	100.76±12.76
SBP percentile	1-99	50.71±31.73
SBP SDS	-2.33-2.33	-0.04±1.19
DBP	40-90	65.18±8.33
DBP percentile	4-99	65.36±23.64
DBP SDS	-1.75-2.33	0.49±0.79

Min: Minimum, Max: Maximum, SD: Standard deviation, SDS: Z-score, BMI: Body-mass index, WC: Waist circumference, WHtR: Weist to height ratio, SBP: Sistolic blood pressure, DBP: Diastolic blood pressure

A positive, statistically significant relationship found between SBP and BMI (r=0.318), WHtR (r=0.170) measurements in children (p<0.05). There was a positive, statistically significant relationship between DBP and BMI (r=0.336), WHtR (r=0.174) in children (p<0.05).

A positive and statistically significant relationship found between SBP and BMI (r=0.257) (p<0.05) in males, and between DBP and BMI (r=0.297) and WHtR (r=0.137) in males (p<0.05). The relationship with SBP for WHtR was not significant (p>0.05). In females, there was a positive and statistically significant relationship between SBP and BMI (r=0.343), WHtR (r=0.182) (p<0.05), and between DBP and BMI (r=0.351), WHtR (r=0.179) (p<0.05) (Table 4).

The study found a significant positive relationship between SBP and BMI (r=0.380), WHtR (r=0.264) in children aged 3-12, and a positive relationship between DBP and BMI(r=0.410), WHtR (r=0.247) in children aged 13 and over (p<0.05), but not significant in children aged 13 and over (p>0.05) (Table 4).

There was a statistically significant difference in terms of BMI, Waist, WHtR in children with different BP levels (p<0.05). BMI (20.29), BMI percentile (83.01), BMI SDS (1.18), waist (70.44), waist SDS (1.8), WHtR (0.51) were the highest in children with HT.

A significant difference found in BMI, Waist, and WHtR among males and females with varying BP levels (p<0.05). Children with HT had the highest BMI, BMI percentile, BMI SDS, waist, waist SDS, and WHtR measurements (Table 5). There was a statistically significant difference in terms of BMI, Waist, WHtR in children aged 3-12 with different BP levels (p<0.05). BMI, BMI percentile, BMI SDS, waist, waist SDS, WHtR were

Table 3. Relationship between demographic and clinical characteristics of children and their gender, age, blood pressure levels

		Age (years) n (%)		Cronic disease n (%)		WHtR n (%)		BMI n (%)				BP n (%)		
		3-12	≥13	No	Yes	No risk	Risky	Under weight	Normal	Over weight	Obese	Normal	High	HT
Gender	Male	300 (73.9)	106 (26.1)	395 (97.3)	11 (2.7)	292 (71.9)	114 (28.1)	48 (11.8)	247 (60.8)	64 (15.8)	47 (11.6)	314 (77.3)	42 (10.3)	50 (12.3)
	Female	256 (74)	90 (26)	339 (98)	7 (2)	282 (81.5)	64 (18.5)	37 (10.7)	259 (74.9)	34 (9.8)	16 (4.6)	306 (88.4)	18 (5.2)	22 (6.4)
p		0.976		0.708		0.002*		<0.001*				<0.001*		
Age (years)	3-12			544 (97.8)	12 (2.2)	416 (74.8)	140 (25.2)	80 (14.4)	363 (65.3)	66 (11.9)	47 (8.5)	438 (78.8)	50 (9)	68 (12.2)
	≥13			190 (96.9)	6 (3.1)	158 (80.6)	38 (19.4)	5 (2.6)	143 (73)	32 (16.3)	16 (8.2)	182 (92.9)	10 (5.1)	4 (2)
p				0.586		0.101		<0.001*				<0.001*		
BP	Normal			604 (97.4)	16 (2.6)	514 (82.9)	106 (17.1)	80 (12.9)	457 (73.7)	51 (8.2)	32 (5.2)			
	High			58 (96.7)	2 (3.3)	40 (66.7)	20 (33.3)	3 (5)	33 (55)	17 (28.3)	7 (11.7)			
	HT			72 (100)	0 (0)	20 (27.8)	52 (72.2)	2 (2.8)	16 (22.2)	30 (41.7)	24 (33.3)			
p				0.395		<0.001*		<0.001*						

*p<0,05 significant relationship; Chi-square test, BMI: Body-mass index, WC: Waist circumference, WHtR: Weist to height ratio, BP: Blood pressure, HT: Hypertension

Table 4. Relationship between SBP, DBP and BMI, WHtR measurements in children according to gender and age

		BMI SDS		WHtR	
		r	p	r	p
Male	SBP	0.257**	<0.001	0.099	0.065
	DBP	0.297**	<0.001	0.137*	0.011
Female	SBP	0.343**	<0.001	0.182**	<0.001
	DBP	0.351**	<0.001	0.179**	<0.001
3-12 years	SBP	0.380**	<0.001	0.264**	<0.001
	DBP	0.410**	<0.001	0.247**	<0.001
≥13 years	SBP	0.065	0.364	0.067	0.353
	DBP	0.018	0.801	0.080	0.265

**p<0.001, *p<0.05 significant relationship, p>0.05 no significant relationship, 0≤r≤0.25 very weak, 0.26≤r≤0.49 weak, 0.50≤r≤0.69 moderate, 0.70≤r≤0.89 strong, 0.90≤r≤1 very strong; Pearson correlation test, BMI: Body-mass index, SDS: Z-score, WHtR: Weist to height ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

the highest in children with HT. No significant difference was found in BMI, waist, and WHtR in children aged 13 and over with different BP levels (p>0.05) (**Table 5**).

In the logistic regression analysis established to determine the factors affecting HT (HT=1: Other:0), the model was found to be statistically significant (X^2=151.540; p<0.001; Nagelkerke R^2=0.390). The logistic regression analysis revealed that age, BMI level, and risky WHtR significantly affect HT (p<0.05). Age was found to be 10.295 times more prevalent in individuals aged 3-12, 13.929 times more in overweight individuals, 13.207 times more in obese individuals, and 3.011 times more in the risky WHTR group. However, the effect was not significant for gender (p>0.05) (**Table 6**).

Table 5. Comparison of BMI, waist circumference, WHtR measurements in children according to blood pressure level in terms of gender and age

		BMI (mean±SD)	BMI percentile (mean±SD)	BMI SDS (mean±SD)	WC (mean±SD)	WC SDS (mean±SD)	WHtR (mean±SD)
BP*	Normal	17.61±3.95	44.19±32.94	-0.27±1.28	64.97±12.51	0.58±1.13	0.46±0.05
Male	High	18.84±3.42	73.05±25.08	0.73±1.02	66.25±11.49	1.16±0.92	0.48±0.04
	HT	20.4±3.3	84.09±21.53	1.25±0.9	71.15±11.08	1.74±1.03	0.52±0.05
p		<0.001*	0.001*	<0.001*	<0.001*	<0.001*	<0.001*
BP*	Normal	17.27±3.6	41.95±29.38	-0.33±1.11	61.63±9.59	0.56±1.02	0.44±0.05
Female	High	17.04±2.59	59.23±29.06	0.18±1.22	60.08±8.03	0.91±1.21	0.48±0.06
	HT	20.03±3.61	80.56±25.74	1.03±1.01	68.84±8.5	1.93±1.11	0.51±0.05
p		<0.001*	<0.001*	<0.001*	0.002*	<0.001*	<0.001*
BP*	Normal	15.96±2.7	38.72±30.88	-0.48±1.23	58.81±7.98	0.46±1.02	0.45±0.05
3-12 years	High	17.5±2.72	68.06±27.79	0.53±1.17	61.33±8.7	1.03±1.06	0.48±0.05
	HT	20.02±2.99	83.75±21.04	1.22±0.86	69.68±9.31	1.81±0.99	0.52±0.05
p		<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
BP*	Normal	21±3.63	53.58±29.59	0.12±1	74.2±10.62	0.82±1.15	0.44±0.06
≥13 years	High	22.3±2.99	73.13±22.34	0.73±0.73	79.75±7.1	1.38±0.71	0.47±0.05
	HT	24.81±6.48	70.41±46.49	0.63±2	83.5±19.02	1.55±2.02	0.49±0.1
p		0.074	0.075	0.12	0.071	0.168	0.069

*p<0.05 significant difference, p>0.05 no significant difference; ANOVA test, SD: Standard deviation, BMI: Body-mass index, SDS: Z-score, WC: Waist circumference, WHtR: Weist to height ratio, BP: Blood pressure, HT: Hypertension

Table 6. Evaluation of factors affecting hypertension according to logistic regression analysis

	B	p	ODDS	95% GA ODDS	
				Bottom	Upper
Gender (male)	0.350	0.261	1.419	0.770	2.616
Age (3-12 years)	2.332	<0.001*	10.295	3.524	30.075
WHtR (risky)	1.102	0.003*	3.011	1.463	6.198
BMI		<0.001*			
Normal	0.400	0.602	1.492	0.332	6.708
Overweight	2.634	0.001*	13.929	2.921	66.418
Obese	2.581	0.002*	13.207	2.569	67.907

*p<0.05 significant effect, p>0.05 no significant effect; Logistic regression, WHtR: Weist to height ratio, BMI: Body-mass index

DISCUSSION

Our study investigated the relationship between BMI, WC, WHtR and BP in children aged 3-18 years. Results showed that prevalence of obese and hypertensive children increased. Males had higher rates of obesit, High BP and HT were more common in children aged 3-12 years, with overweight, obese, and WHtR risky individuals.

Obese people prevalence worldwide is increasing, with the World Obesity Atlas 2023 predicting a rise from 10% to 20% in males and 8% to 18% in females by 2035.[2] According to WHO data, the rate of obese children and adolescents aged 5-19 rose from 4% in 1975 to 18% in 2016.[1] In China, obese prevalence increased from 2.51% to 10.56% between 2000 and 2019, resulting in a total prevalence of overweight and obesity from 9.81% to 25.88%.[12]A 2015 study on 5206 children in seven European countries (Turkiye, Bulgaria, Romania, Lithuania, Germany, Italy, and Netherlands) revealed that 15.6% were overweight and 4.9% obese. Romanian children had the highest prevalence of obesity, while Italian children had the lowest. Turkish children had the second highest obesity rate in Europe, at 7.7%.[13] In the United States (USA), the obesity rate was 21.4% in males and 21.6% in females.[14] Based on studies conducted in our country over a 20-year period, obesity rates were shown to be 1.3% in the 2000s, 3.7% in 2009, 7.9% in 2013, and 11.8% in 2022.[1,15,16] According to data from research conducted in our country, the obesity rate ranges between 4.4% and 13%.[16] In our study, 8.4% of the children were obese and 13% were overweight, indicating that roughly one in every five children is obese or overweight. The reasons for this increase in obese prevalence in our study may include decreased physical activity and increased energy intake due to changes in eating habits. Furthermore, the widespread use of technological devices that easily fill free time (smart phones, televisions, computers, etc.) contributes significantly.[1] Obese children prevalence is higher in our study than in the general population, lower than in the USA, but comparable to the findings in Turkiye. The high rates in the USA could be attributed to the country's increased intake of fast food and convenience meals.[14] The prevalence of obesity in Western Europe decreases due to increased public health studies and expenditures.[13] To prevent the epidemic, more emphasis should be placed on programs promoting healthy nutrition, active lifestyles, school activities, and sports in children.[1] According to WHO data, males have a higher obesity rate (8%) than females (6%), and this is also observed in our study (11.6% of males and 4.6% of females).[1] This is likely due to males spending more time on screens and playing video games, leading to a decrease in physical activity.[14]

We found that high BP was present in 8.0% of children and high HT in 9.6%. An increasing trend in the prevalence of childhood HT has been observed in the last 20 years. However, there are few global studies on childhood HT prevalence. In 2019, a meta-analysis found a 4% HT rate and 9.7% high BP rate among children aged 19 and under.[17] We found a two-fold increase in HT rates compared to the 2019 meta-analysis. Childhood HT prevalence in Turkiye varies between 8.5% and 15%, with rates ranging from 4.4% in Sivas in 2004, 5.4% in Bursa in 2007, and 7.9% in Ankara in 2014.[5,18-20] Studies show an increase in HT over the years, attributed to factors such as obesity, increased salt and calorie consumption, lack of physical activity, and stress. The prevalence of HT in Turkiye has been observed to rise due to factors such as obesity, increased salt and calorie consumption, and stress.[18-20]

In our study, males had a higher rate of high BP and HT than females, which is consistent with prior research in our nation and around the World.[18,21,22] This is related to variables such as obesity and computer game addiction, which make males more inactive and prone to high BP. The findings challenges the widely held belief that BP rises with age and body size in children.[23] High BP and HT were more common in children aged 3 to 12, but low BP and HT were more common in children aged 13 and over. This could be attributed to a reduced, less equal population dispersal over 13 years. A study conducted in India in 2022 found that, similar to our study, the increase in BP was inversely correlated with age.[24]

Some studies conducted to establish the best anthropometric predictor of HT risk in children discovered a substantial association between WC and HT.[22] In a study of Chinese children aged 9 to 17, a greater prevalence of HT was seen in abdominal obesity, particularly in young children with high WC, compared to those with normal WC.[25] To determine whether WC is a predictor of cardiovascular complications in children, a study of 160 overweight/obese children and adolescents aged 6-18 years found that visceral obesity in children was not a risk factor for vascular or heart failure, but it was a significant predictor in adolescents.[26]

In our study, we observed that WC and WC SDS measurements were high in children with HT between the ages of 3 and 12 years. A significant relationship was found between HT and WC in this age group, but no significant relationship was found in children over 13. The findings suggest that WC is an effective method for predicting HT in childhood, but its accuracy may be limited by the positive relationship between WC and height.[9] Long-term monitoring is crucial to prevent cardio-metabolic complications.

A Korean study discovered that the WHtRis useful in predicting cardiometabolic risk in normal-weight and overweight children.[27] Males had a higher risky WHtR (28.1%) than females (18.5%), and high-risk children (HT) were found in 72.2% of those with a risky WHtR in our study. Our findings indicate that the WHtR is a highly useful indicator for predicting HT. A favorable link was discovered between SBP, DBP, and WHTR, with slight variations according on gender and age. We found a significant positive relationship between WHtR and SBP in both gender, but no significant relationship

with SBP in males. WHTR had a significant relationship with SBP/DBP in the 3-12 age group, but no significant relationship over 13. HT was seen in 72.1% of children with a risky WHtR in the 3-12 age group and 75% of children over 13. This difference may be due to changes in physical and hormonal structures during adolescence.

According to research, there is a significant link between high BMI and WHtR and high BP in young children.[18-20] Similarly, high BMI in adolescence has been shown to be a powerful indication of adult obesity and HT risk, can be utilized to avoid cardiometabolic diseases.[5] These findings underscore the importance of understanding the link between obesity and HT in health policies and prevention strategies, emphasizing the need for targeted interventions to prevent cardiometabolic diseases.[18-20] A study in Korea found that WHtR was higher than BMI in defining cardiometabolic diseases among overweight adolescents. Metabolic syndrome was more common in those with WHtR ≥0.5.[27] Our study supported these findings; HT risk was 13.207 times higher in obese individuals according to BMI and 3.011 times higher in those with WHTR ratio ≥0.5. However BMI was found to be superior to WHtR in predicting HT in our research.

Obesity was discovered in 10.5% of females and 13.9% of males with HT in a 2010 study conducted in Turkiye to investigate the frequency of asymptomatic HT in school-age children.[28] In a 2014 Ankara study, overweight and obesity were shown to be more prevalent in males.[21] Similarly, in our study, obese males (38%) had a higher HT rate than obese females (22.7%). Obesity is thought to be the primary risk factor for developing HT, according to studies.[21,28-30] Our study reveals that obesity and an increased WHtR increase the risk of HT in children, emphasizing the need to prevent and treat childhood obesity to prevent further complications.

Limitations

The study sample, consisting of a small number of children in a single region, primarily males, does not exhibit a homogeneous distribution between genders. Additionally, the number of children over 13 years old is also less, indicating a lack of uniformity in the distribution.

CONCLUSION

In conclusion, we discovered that children aged 3 to 12, overweight, obese, risky WHtR had a higher HT rate. BMI was more important than WHtR in predicting high BP ve HT in children. Therefore controlling obesity and the WHtR is critical for preventing HT development. Regular BP monitoring is critical for early detection and intervention. Developing health policies and prevention initiatives for childhood obesity and HT can help to lower adult obesity and cardiovascular problems.

ETHICAL DECLARATIONS

Ethics Committee Approval

The Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee approved the study (Date: 12.09.2022, Decision No: 146/25).

Informed Consent

Families of all children signed the informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Case Report

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Renal CT angiography findings of bilateral double renal artery: a preliminary pediatric case report

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ABSTRACT

Double renal arteries are among the renal vascular variations. Among renal morphological variations, the most commonly encountered are variations in the number of renal arteries, with double renal arteries being the most frequent. The present pediatric case provides information on rare occurrence of bilateral double renal artery. Computed tomography angiography showed bilateral double renal artery in a 11 year old boy while investigating the etiology of hypertension. Also digital subtraction angiography confirmed the diagnosis. The case report raise the awareness among clinicians regarding the variations in the kidney's blood supply.

Keywords: Pediatric, hypertension, bilateral double renal artery

INTRODUCTION

Double renal arteries are among the renal vascular variations.[1] Variations regarding these renal arteries have been related to embryological development of vessels. Among renal morphological variations, the most commonly encountered are variations in the number of renal arteries, with double renal arteries being the most frequent.[2] Chugh et al.[3], in a study of 170 human kidneys, reported that 21.2% had double renal arteries. Similarly, Goscicka et al.[4], in a study of 140 human fetuses, found that 21.3% of the cases exhibited double renal arteries. Many studies focus on unilateral double renal arteries, but here we present a rare pediatric case with bilateral double renal arteries.

CASE

Incidental hypertension was discovered in an 11 year old boy during pre-anesthesia assessment for genu valgum surgery. He had no hypertension associated complaints and symptoms. Examination showed a pulse rate of 85 per minute, blood pressure was 200/100 mmHg. There was no radiofemoral delay and peripheral pulses were well palpable. His weight was 45 kg (>75-90p), height 143 cm (50p), BMI 22 kg/m^2. The fundus examination showed retinal arteries that indent the retinal veins suggestive of hypertensive retinopathy grade 2. Blood chemistry results were as follows: blood urea 34 mg/dl, creatinine 0.7 mg/dl, triglyceride 154mg/dl, cholesterol 172 mg/dl. Free T4 and TSH were in the normal range. Urinary microscopy and stick examination were unremarkable. Doppler ultrasound did not show features of main renal artery stenosis, however the left kidney was slightly smaller (hypoplasia). Abdomen computed tomography angiography showed normal main renal arteries, with bilateral accessory renal arteries originating from the abdominal aorta (**Figure a, b**). Decreased calibration was detected at the left renal accessory artery feeding the lower pole of the left kidney. The patient was treated with amlodipine 0.5 mg/kg and losartan/hydrochlorothiazide 50/12.5 mg. On follow up after 1 week, the patients blood pressure ranged between 138/95 and 145/96 mm Hg. A beta blocker was added (metoprolol). During his follow up period a digital subtraction angiography (DSA) was performed, which also showed bilateral double renal arteries.

Figure a, b. Bilateral accessory renal arteries originating from the abdominal aorta (red arrows)

DISCUSSION

Knowledge of the variations of renal vascular anatomy is important in the exploration and treatment of renal trauma, renal transplantation, renovascular hypertension, renal artery embolization, angioplasty or vascular reconstruction for congenital and acquired lesions, surgery for abdominal aortic aneurysm and conservative or radical renal surgery.[5] The present case provides information on the rare occurrence of bilateral double renal artery. Dhar and Lal[6] studied the renal vasculature in 40 cadavers and revealed multiple renal arteries in 20% of cadavers, unilateral anomaly was more common (15%) than bilateral (5%). In another study, multiple renal arteries were found bilaterally in 10.2% of donors and unilaterally in 20.8%, resulting in a total incidence of 31%.[1] Bordei et al.[2] demonstrated bilateral double renal arteries in 6 out of 54 cases where double renal arteries originated from the aorta. It is important to be aware that accessory renal arteries are end arteries; consequently, during renal surgical procedures, besides hemorrhage and loss of renal parenchyma, arterial lesions may induce segmental ischemia followed by hypertension.

CONCLUSION

The presence of double renal arteries increases the complexity of renal transplantation, kidneys with double arterial supply being involved in a higher percentage of transplant failures than normal kidneys. So that arteriography should be performed in such cases. So that our case report raise the awareness among clinicians regarding the variations in the kidney's blood supply.

ETHICAL DECLARATIONS

Informed Consent

The patient's parents signed a free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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