Turkish Journal of Pediatric Disease
Türkiye Çocuk Hastalıkları Dergisi

Is There a Relationship Between Urinary Tract Infections and Vitamin D and Cathelicidin Levels?: A Cross-Sectional Observational Study From the Pediatric Emergency Department

İdrar Yolu Enfeksiyonları ile D Vitamini ve Katelisidin Düzeyleri Arasında Bir İlişki Var mı?: Çocuk Acil Servisinden Kesitsel Gözlemsel Bir Çalışma

Alper ÇİÇEK[1], Pelin ELİBOL[1], Banu İŞBİLEN BAŞOK[2], Dilek ORBATU[3], Emel BERKSOY[1], Demet ALAYGUT[4], Oya BALTALI HIDIR[3]

[1]Department of Pediatric Emergency, University of Health Sciences, İzmir Tepecik Education and Research Hospital, İzmir, Türkiye
[2]Department of Medical Biochemistry, University of Health Sciences, İzmir Tepecik Education and Research Hospital, İzmir, Türkiye
[3]Department of Pediatric, University of Health Sciences, Izmir Tepecik Education and Research Hospital, İzmir, Türkiye
[4]Department of Pediatrics Division of Pediatric Nephrology, University of Health Sciences, Izmir Tepecik Education and Research Hospital, İzmir, Türkiye

ABSTRACT

Objective: Cathelicidin is a crucial antibacterial peptide that is produced in the urinary system and is induced by vitamin D. In order to distinguish between lower and upper urinary tract infections (UTIs), the association between cathelicidin levels and vitamin D levels was examined in this study.

Material and Methods: We analyzed complete blood count, biochemistry profile, C reactive protein (CRP), 25 hydroxyvitamin D, serum cathelicidin levels of pre-treatment children aged 0-18 years who were diagnosed with a UTI in the Pediatric Emergency Room.

Results: A total of 72 children (36 healthy and 36 patients) were included in the study. The mean age of the participants was 83.8±66.22 months, with 40 (56%) female and 32 (44%) male. Our patient group had higher white blood cell, neutrophil, and CRP levels than our control group (p=0.050). There was no significant difference in cathelicidin levels (5.7±3.7; 9.6±10.9; p=0.810) or vitamin D levels (23.3±9.5; 25.9±12.5; p=0.795) between patients with lower and upper UTI. We found a positive correlation between vitamin D and cathelicidin levels in the control group (r=0.346, p=0.030). There was no statistically significant difference in cathelicidin levels between patients with upper UTI and the control group (p=0.054).

Conclusion: Although there was no significant relationship between vitamin D and cathelicidin levels in children with urinary tract infections, a weak but positive correlation exists between vitamin D and cathelisidin in healthy children.

Key Words: Cathelicidin, Emergency, Pediatric, Urinary tract infection, Vitamin D

ÖZ

Amaç: Katelisidin, üriner sistemde üretilen ve D vitamini tarafından indüklenen önemli bir antibakteriyel peptittir. Bu çalışmada alt ve üst idrar yolu enfeksiyonlarını (İYE) ayırt etmek için katelisidin düzeyleri ile D vitamini düzeyleri arasındaki ilişki incelenmiştir.

0000-0001-5017-4525 : ÇİÇEK A
0000-0002-2195-7421 : ELİBOL P
0000-0002-1483-997X : İŞBİLEN BAŞOK B
0000-0002-5716-2938 : ORBATU D
0000-0002-6831-1353 : BERKSOY E
0000-0002-2164-4652 : ALAYGUT D
0000-0002-0062-9138 : BALTALI HIDIR O

Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. This study was approved by the ethics committee of Izmir Tepecik Training and Research Hospital (15.06.2021-2021/06-52).

Contribution of the Authors / Yazarların katkısı*: *ÇİÇEK A: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study. ***ELİBOL P:*** Taking responsibility in necessary literature review for the study. ***İŞBİLEN BAŞOK B:*** Reviewing the article before submission scientifically besides spelling and grammar. ***ORBATU D:*** Taking responsibility in necessary literature review for the study. ***ALAYGUT D:*** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar. ***BALTALI HIDIR O:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Taking responsibility in necessary literature review for the study, Reviewing the article before submission scientifically besides spelling and grammar.

How to cite / *Atıf yazım şekli* : Çiçek A, Elibol P, İşbilen Başok B, Orbatu D, Berksoy E, Alaygut D, et al. Is There A Relationship Between UTI and Vitamin D and Cathelicidin Levels?: A Cross-Sectional Observational Study From the Pediatric Emergency Department. Turkish J Pediatr Dis 2024;18:174-180.

Correspondence Address / Yazışma Adresi:
Alper ÇİÇEK
Department of Pediatric Emergency,
University of Health Sciences,
İzmir Tepecik Education and Research Hospital, İzmir, Türkiye
E-posta: dr_alper_cicek@hotmail.com

Received / Geliş tarihi : 26.09.2023
Accepted / Kabul tarihi : 19.01.2024
Online published : 15.02.2024
Elektronik yayın tarihi
DOI: 10.12956/tchd.1366493

Gereç ve Yöntemler: Çocuk Acil Servisinde idrar yolu enfeksiyonu tanısı alan 0-18 yaş arası tedavi öncesi çocukların tam kan sayımı, biyokimya profili, C reaktif protein (CRP), prokalsitonin, 25 hidroksivitamin D ve serum katelisidin düzeylerini analiz ettik.

Bulgular: Çalışmaya toplam 72 çocuk (36 sağlıklı ve 36 hasta) dahil edildi. Katılımcıların yaş ortalaması 83.8±66.22 ay olup, 40'ı (%) kadın, 32'si (%) erkektir. Hasta grubumuzun beyaz küre, nötrofil ve CRP düzeyleri kontrol grubumuza göre daha yüksekti (p=0.050). Alt ve üst İYE'li hastalar arasında katelisidin düzeyleri (5.7±3.7; 9.6±10.9; p=0.810) veya D vitamini düzeyleri (23.3±9.5; 25.9±12.5; p=0.795) açısından anlamlı fark yoktu. Kontrol grubunda D vitamini ile katelisidin düzeyleri arasında pozitif korelasyon bulduk (r=0.346; p=0.030). Üst İYE'li hastalar ile kontrol grubu arasında katelisidin düzeyleri açısından istatistiksel olarak anlamlı fark yoktu (p=0.054).

Sonuç: İdrar yolu enfeksiyonu olan çocuklarda D vitamini ile katelisidin düzeyleri arasında anlamlı bir ilişki bulunmazken, sağlıklı çocuklarda D vitamini ile katelisidin arasında zayıf fakat pozitif bir ilişki bulunmaktadır.

Anahtar Sözcükler: Katelisidin, Acil, Pediatri, Üriner sistem enfeksiyonu, Vitamin D

INTRODUCTION

Although based on observational research, it has been proposed that adequate vitamin D intake throughout childhood lowers levels of TNF-, C-reactive protein (CRP), and IL-6 and prevents the spread of inflammation. According to several epidemiological research, vitamin D insufficiency is linked to a variety of conditions outside those that affect the musculoskeletal system. Food allergies, hypertension, hyperglycemia, metabolic syndromes, and upper respiratory tract infections are all linked to decreased serum 25-hydroxyvitamin D3 (25(OH)D3) levels (1- 5). Recently, there was a correlation between vitamin D deficiency (serum 25(OH) D3 level 20 ng/mL) and recurrent urinary tract infections in children (6). Cathelicidin is a bactericidal agent that clears off intracellular mycobacteria and has a regulatory role in multiple different processes of autophagy activity. It helps positively to the fusion of mycobacterial phagosomes, autolysosomes, and autophagosomes (7,8). Also, it can stimulate chemokine and cytokine production with the help of various cell types. Its expression in neutrophils, monocytes, epithelial cells and macrophages is stimulated by 1,25 dihydroxyvitamin D (1, 25(OH)2D). Studies on urinary tract infections (UTI) have revealed that it is crucial for safeguarding the urinary tract (9,10). In addition, it is estimated that the defense system of the urinary tract may largely depend on some mediators, which are specifically soluble and epithelial cell-derived. It is presumed to be induced by bactericidal antimicrobial peptides such α, β-defensins, and cathelicidin (11,12). It is known that when exposed to *E. coli,* bladder and renal epithelial cells release cathelicidins, specifically LL-37 in humans (13,14). Cathelicidin and vitamin D levels in pediatric patients with upper or lower urinary tract infections were compared in this investigation before treatment. To find out the connection between the type and severity of urinary tract infections, they were compared with healthy controls.

MATERALS and METHODS

In this case control research, individuals with UTI who were hospitalized at the University of Health Sciences, İzmir Tepecik Hospital, Emergency Medicine Clinic between June and December 2021 were included. Prior to therapy, the values of the complete blood count, biochemistry profiles, C-reactive protein, procalcitonin, and 25(OH)D3 and serum cathelicidin levels were examined. Patients with immunological deficiencies, anatomical or functional abnormalities of the urinary system, or diabetes mellitus were excluded. All patients who participated in the study provided written and verbal consent. The patients' demographic data, UTI type (lower/upper), urine analysis outcomes, and results of blood tests were documented. Patients with at least one of the following symptoms of upper urinary tract infection (UTI) flank pain, costovertebral angle tenderness, fever, abdominal pain, the presence of pyuria/nitrite in the urine as well as growths of ≥50.000 CFU/ml in the catheter culture and ≥100.000 CFU/ml in the midstream urine were considered to have an upper UTI. In infants and young children, UTI usually presents with nonspecific symptoms and signs (e.g. fever, irritability, vomiting, diarrhea, poor feeding). Fever may be the sole manifestation of UTI in infants and children <2 years of age. Urine nitrite and bacteriuria positivity and significant growth in urine culture were accepted as upper UTI even if the infants had fever condition and nonspecific symptoms. Patients with at least one of the following symptoms, as well as pyuria (≥5 leukocytes per high magnification in urine microscopy), nitrite, and ≥50.000 CFU/ml in catheter culture, ≥100.000 CFU/ml in midstream pee a growth of CFU /ml were classified as having a lower UTI. Serum 25 (OH) D3 levels were classified as follows: normal ≥ 30ng/ml, deficient 20-30 ng/mL, and severely deficient < 12ng/mL (14). Age and gender-matched healthy children whose blood samples were taken during routine control were included in the control group (Group 2). Plain blood collection tubes (BCTs) (BD Vacutainer® SST II Advance Tube, 5mL, 13x100 mm, USA) were used to collect venous blood samples. Within an hour of blood collection, serum samples were isolated from cellular debris by centrifugation for 10 minutes at 1.500 g. Before further investigation, serum samples were divided into smaller amounts and kept at 80 °C.

Serum cathelicidin concentrations were determined by a commercial "Human LL37(Anti-bacterial protein LL-37)" kit employing quantitative sandwich enzyme immunoassay technique (Elabscience, Houston, TX, USA)(Catalog No: E-EL-H2438). In accordance with the manufacturer's instructions, the analysis was completed. The kit's CVs (coefficients of variation) were less than 10% both within and

between assays. The test's limit of detection (LOD) was 0.94 ng/mL.

Serum 25-OH-Vitamin D levels were measured by an immunoassay analyzer (Advia Centaur XP; Siemens Healthineers, Siemens Healthcare GmbH, Germany) according to the manufacturers' instructions.

This study was approved by the ethics committee of Izmir Tepecik Training and Research Hospital (15.06.2021-2021/06-52). Every method carried out during the study complied with the Declaration of Helsinki's guiding principles as well as the institutional and national research committee's ethical requirements.

Statistical Analysis

Using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA), a statistical software product, we assessed the data. For descriptive statistics, the frequency (n), percentage (%), mean and standard deviation were all given. The Shapiro Wilk test of normality and Q-Q graphs were used to assess the normal distribution of the numerical data. Using Levene's test, we looked at the homogeneity of variances. Independent samples T test was used to compare the means of two independent groups consisting of normally distributed continuous data. Differences between two groups which were not normally distributed were examined with the Mann-Whitney U Test. For categorical data, Pearson's chi-square test and Fisher's exact test were used. Correlations were assessed using the Spearman's correlation test. A p value less than 0.05 was considered statistically significant.

RESULTS

A total of 72 children were included in the study. Thirty-six of these children (n=22 girls (61.1%), n=14 boys (38.9%)) with a mean age of 50.4±53.8 months were in the patient group diagnosed with UTI, and 36 of them (n=18 girls (50%), n=18 boys (50%)) with a mean age of 117.2±60.8 months were in the healthy group. Age and gender did not significantly difference between the patient and control groups (p=0.343) (Table I).

Fever was experienced by 29 patients (80.6%) and stomach pain by 16 patients (44.4%) as the most frequent UTI symptoms.

Table I: Demographic data, patient symptoms and types of UTI in the study group

Demographic data of study subjects	UTI group n: 36	Control group n: 36	p
Age (mean±SD) (months)	50.40±53.84	117.27±60.82	0.343
Sex (girl/boy)	22/14	18/18	0.920
Type of UTI n(%)			
Lower UTI	7 (19.4)	7 (19.4)	
Upper UTI	29 (80.6)	29 (80.6)	

UTI: *Urinary tract infections*

The presence of an unpleasant odor, suprapubic pain, dysuria, frequent urination, and flank pain were other symptoms (Table II).

The most frequent etiological agent identified in 25 patients (69.4%) with substantial growth in urine culture was *Escherichia coli* (18/69.2%). We found that patients with significant growth in the urine culture had significantly higher white blood cell counts, urinary nitrite positivity, and only abdominal pain symptoms at admission when compared to patients without growth (p<0.050) (Table II).

Comparing the UTI group to the healthy group, WBC, neutrophil count, and C reactive protein (CRP) levels were higher in the UTI group (p<0.050) (Table III).

Cathelicidin and vitamin D levels did not differ significantly between lower and upper UTI (p=0.810 and p=0.795, respectively) (Table IV). Cathelicidin levels (9.6±10.9) in patients with upper UTI did not differ significantly from the control group (5.2±5.7) (p=0.054) . There was a positive correlation between cathelicidin and vitamin D levels in the control group (r=0.346; p=0.030) (Figure 1).

DISCUSSION

UTI is a frequent and dangerous bacterial illness identified by pediatricians (15). The infection can spread to the lower urinary tract (cystitis) or the upper urinary tract (pyelonephritis). Unfortunately, based on clinical signs and symptoms in infants and young children, it can be challenging to distinguish pyelonephritis from cystitis (16). Uncircumcised boys have a 10 to 12-fold increased risk of developing a UTI during the first six months of life. Above the age of one, girls are more prone to develop an UTI than the boys (13,16). Similar to the literature, there are a lot of girls in our study. The most typical sign in the first two years of life is unexplained fever (13,14). Non-specific symptoms include irritability, malnutrition, recurrent abdominal pain, vomiting, anorexia, and growth retardation (17). After the second year of life, UTI symptoms and indicators become increasingly obvious. Signs and symptoms of pyelonephritis include chills, fever, malaise, vomiting, costovertebral angle tenderness, flank pain, and back pain, lower urinary tract signs and symptoms include abdominal or suprapubic pain or tenderness, dysuria, cloudy urine, foul-smelling urine, increased urinary frequency, daytime wetting, new-onset nocturnal enuresis (13,17,18). In our study, we recorded the symptoms of the patients at admission: abdominal pain, foul-smelling urine odor, and fever were the most common symptoms in the literature. Most UTIs occur in the lower urinary tract, and only a tiny percentage of them progress to pyelonephritis (19). In contrast to the literature, our investigation revealed that pyelonephritis was more prevalent. The distinction might exist because our hospital is the only pediatric tertiary care facility in the area. As a result, patients with conditions like pyelonephritis

Table II: Comparison of patients with and without growth in urine culture

Variables	Culture Growth Yes	Culture Growth No	Total	p
Parameters, mean (SD)				
WBC(×10³/mm) (n=34)	13.42±4.25	9.44±3.55	12.25±4.40	0.023*
CRP (mg/L) (n=35)	53.86±71.92	29.80±54.19	46.98±67.46	0.324*
D vitamin (n=36)	25.90±13.10	24.53±9.15	25.48±11.91	0.932*
Cathelicidin (n=36)	8.79±10.11	9.16±10.47	8.90±10.07	0.904*
Neutrophil/lymphocyte ratio (n=34)	3.61±4.17	3.62±3.22	3.61±3.87	0.558*
Urine test(n=36)				
pH	5.82±0.73	5.68±0.78	5.77±0.74	0.383*
Density	1021.04±9.98	1023.91±10.10	1021.92±9.96	0.419*
Pyuria				
Yes	23 (69.7)	10 (30.3)	33 (91.6)	
No	2 (66.7)	1 (33.3)	3 (8.3)	1.000‡
Nitrite				
Yes	14 (93.3)	1 (6.7)	15 (41.6)	
No	11 (52.4)	10 (47.6)	21 (58.3)	0.011‡
Proteinuria				
Yes	19 (67.9)	9 (32.1)	28 (77.7)	
No	6 (75)	2 (25)	8 (22.2)	1.000‡
Symptoms (n=36)				
Fever				
Yes	22 (75.9)	7 (24.1)	29 (80.5)	0.167‡
No	3 (42.9)	4 (57.1)	7 (19.4)	
Dysuria				
Yes	2 (50)	2 (50)	4 (11.1)	0.570‡
No	23 (71.9)	9 (28.1)	32 (88.8)	
Flank pain				
Yes	1 (50)	1 (50)	2 (5.5)	0.524‡
No	24 (70.6)	10 (29.4)	34 (94.4)	
Frequent urination				
Yes	1 (50)	1 (50)	2 (5.5)	0.524‡
No	24 (70.6)	10 (29.4)	34 (94.4)	
Urgency				
Yes	0	0		-
No	25 (69.4)	11 (30.6)	36 (100)	
Abdominal pain				
Yes	8 (50)	8 (50)	16 (44.4)	0.034‡
No	17 (85)	3 (15)	20 (55.5)	
Foul-smell odor				
Yes	9 (90)	1 (10)	10 (27.7)	0.127‡
No	16 (61.5)	10 (38.5)	26 (72.2)	
Suprapubic pain				
Yes	4 (66.7)	2 (33.3)	6 (16.6)	1.000‡
No	21 (70)	9 (30)	30 (83.3)	

***:** *Mann-Whitney U test,* **‡:** *Chi-square test, Fisher's Exact test,* ***CRP:** C-reactive protein,* ***WBC:** White blood cell*

who need more in-depth follow-ups are sent to our facility. Another factor is that patients with low sociocultural levels who applied to our facility might not have been accepted because they were unable to express their concerns or symptoms clearly.

In patients with suspected UTIs, we measured the erythrocyte sedimentation rate (ESR), CRP, or procalcitonin level (PCT). Acute pyelonephritis is indicated by neutrophils, high serum ESR, high serum CRP, and elevated white blood cells in the urine sediment. These tests, however, have a limited level of specificity and are unable to distinguish between acute pyelonephritis and lower urinary tract infection (20,21). Sensitivity varies from 81 to 93% and specificity from 37 to 76% in a meta-analysis of studies examining the reliability of PCT, CRP, and ESR levels in predicting dimercaptosuccinic acid-confirmed pyelonephritis in children with culture-confirmed UTIs. Although CRP 20 mg/L (2 mg/dL) and PCT>0.5 ng/mL (0.5 mcg/L) seem to be useful in eliminating and confirming pyelonephritis, respectively, the studies do not guarantee the outcomes (22). As expected, the UTI group in this study had higher levels of WBC and CRP. Only CRP values were found to be greater in the upper UTI group in the comparison between lower and higher UTIs, which is an remarkable finding.

Table III: Comparison of laboratory findings between UTI and control group

Variables	UTI (Group 1)	Control (Group 2)	Total	p*
CBC parameters, mean (SD)				
WBC(×10³/mm)	12.25±4.41	8.80±3.31	10.50±4.23	<0.001
Hemoglobin	11.19±1.71	12.13±1.21	11.66±1.54	0.010
Platelet count (×10³/µl)	330.50±122.05	287.06±79.42	308.46±104.21	0.086
Neutrophil count (×10³/uL)	7.22±4.57	5.18±2.93	6.18±3.93	0.033
Lymphocyte count (×10³/uL)	3.69±2.49	2.77±1.44	3.22±2.07	0.068
Neutrophil/lymphocyteratio	3.61±3.87	2.57±2.53	3.09±3.28	0.194
Other parameters, mean (SD)				
BUN (U/L)	21.20±9.18	23.08±5.94	22.13±7.75	0.313
Creatinin (U/L)	0.48±0.16	0.60±0.15	0.54±0.16	0.003
AST (ng/L)	34.60±22.18	26.60±10.63	30.60±17.73	0.059
ALT (µg/L)	19.82±21.72	16.85±9.09	18.34±16.59	0.458
CRP (mg/L)	46.98±67.46	1.75±2.11	25.03±53.20	<0.001
D vitamin	25.48±11.91	26.82±9.71	26.15±10.81	0.603
Cathelicidin	8.90±10.07	5.20±5.77	7.05±8.36	0.061

***:** *Student t test,* ***ALT:** *Alanine aminotransferase,* ***AST:** *Aspartate aminotransferase,* ***BUN:** *Blood urea nitrogen,* ***CBC:** *Complete blood count,* ***CRP:** *C-reactive protein,* ***UTI:** *Urinary tract infections ,* ***WBC:** *White blood cell*

Table IV: Comparison of laboratory findings between Lower UTI and Upper UTI group

Variables	Lower UTI group	Upper UTI group	Total	p*
CBC parameters, mean (SD)				
WBC(×10³/mm)	9.30±4.17	12.75±4.31	12.25±4.41	0.061
Hemoglobin	12.52±2.37	10.95±1.50	11.19±1.71	0.098
Platelet count (×10³/µl)	243.80±88.63	345.44±121.90	330.50±122.05	0.061
Neutrophil count (×10³/uL)	4.52±3.84	7.68±4.58	7.22±4.57	0.138
Lymphocyte count (×10³/uL)	3.30±1.71	3.76±2.62	3.69±2.49	0.789
Neutrophil/lymphocyte ratio	1.92±1.73	3.90±4.08	3.61±3.87	0.319
Other parameters, mean (SD)				
BUN (U/L)	20.50±15.1	21.34±7.81	21.20±9.18	0.335
Creatinin (U/L)	0.42±0.11	0.49±0.16	0.485±0.16	0.251
AST (ng/L)	37.50±17.10	34.00±23.30	34.60±22.18	0.614
ALT (µg/L)	16.33±9.50	20.55±23.53	19.82±21.72	0.568
CRP (mg/L)	2.33±3.38	56.22±70.77	46.98±67.46	0.015
D vitamin	23.38±9.52	25.99±12.51	25.48±11.91	0.795
Cathelicidin	5.73±3.77	9.67±10.98	8.90±10.07	0.810

***:** *Many Whitney U,* ***ALT:** *Alanine aminotransferase,* ***AST:** *Aspartate aminotransferase,* ***BUN:** *Blood urea nitrogen,* ***CBC:** *Complete blood count,* ***CRP:** *C-reactive protein,* ***UTI:** *Urinary tract infections ,* ***WBC:** *White blood cell*

For UTI diagnosis, urine culture is still the gold standard (23). The most prevalent germ responsible for 80–90% of UTIs in children is *Escherichia coli* (13,18). Our culture results showed a large proportion of *Escherichia coli* growth, similar to the literature.

There was no growth in urine culture in some of the cases who presented with high fever and did not have a specific fever focus but were accompanied by upper urinary tract infection symptoms. However, pyuria and bacteriuria were present in the urine.

Culture negativities were attributed to the fact that some of the cases came with antibiotic treatment and some of them did not have laboratory-induced reproduction.

Cathelicidin is a protein that is produced by neutrophils, bone marrow cells, and epithelial cells and is encoded by the antimicrobial protein (CAMP) gene. It is antibacterial and effective against viruses and bacteria. It is a chemical molecule for attracting defense cells by interacting with fMLP (N-formyl-methionyl peptides) receptors (13, 24). Human cationic antimicrobial protein 18 (hCAP18) is one of the members of the cathelicidin family which is found in humans. LL-37, on the other hand, is an alpha-helical peptide produced by splitting the C-terminal end of the hCAP18 protein by serine proteases and proteinase 3 (25). Hacihamdioglu et al. (26) analyzed the relationship between cathelicidin and vitamin D in UTI in their study; they found no significant difference between the study and healthy groups in terms of UTI and cathelicidin levels. They connected elevated cathelicidin levels during UTIs to insufficient vitamin D levels. They discovered a link between vitamin D and cathelicidin levels in both people with urinary tract infections and healthy people. A similar study found a positive association between vitamin D levels and cathelicidin levels (27). In our study, we compared children with UTI and healthy controls. There was

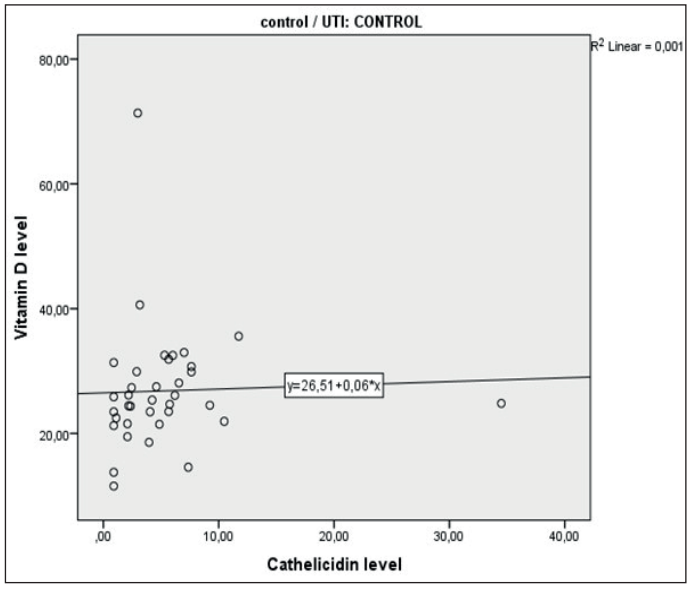

Figure 1: Cathelicidin - vitamin D correlation graphic in control group

no significant difference between vitamin D-cathelicidin levels in UTIs. Likewise, we found no discernible variation in vitamin D and cathelicidin levels between patients with upper and lower UTIs. There were no differences in cathelicidine and vitamin D levels between upper UTI patients and the control group. We hypothesized that it might be because there weren't enough patients with upper UTI. However, in the healthy group, we discovered a significant association between vitamin D and cathelicidin levels, which is consistent with previous research.

Numerous research have been done on the role of vitamin D and cathelicidin as biomarkers in individuals with asthma, cystic fibrosis, *Staphylococcus aureus*, *Clostridium difficile*, and UTIs (28,29). A study found no correlation between blood hCAP18/LL-37 levels and pulmonary conditions, the *Mycobacterium avium* complex, or serum vitamin D levels (30). Also, there was no correlation between vitamin D levels in the bronchoalveolar lavage fluids of children with cystic fibrosis and the production of LL-37, the only human antimicrobial peptide of the cathelicidin family (31). But another study concluded that serum cathelicidin correlated with vitamin D levels, and they were associated with a reduced frequency of UTIs in younger children (27). In addition, another study utilizing a model of acute infection with non-typeable *Haemophilus influenza* shown that infection and lung inflammation cleared more quickly in vitamin D-deficient animals due to elevation of cathelicidin-related antimicrobial peptide (32). These findings suggest that during infection, in vivo cathelicidin synthesis is controlled by vitamin D-dependent and independent mechanisms. It depends on the bacterial species, cell types, and immune status of the host. In our investigation, serum cathelicidin levels were greater in the UTI group than in the control group, although this difference did not reach statistical significance. This might be because there aren't enough patients in the upper UTI group and because their cathelicidin levels are higher. We wanted to increase the number of patients. But due to the pandemic and the expiry date of cathelicidine kits approaching, we had to study the collected patient samples. Our study's limitations include an insufficient sample size of UTI and control group patients with low vitamin levels and an absence of information about pre-disease vitamin D and cathelicidin levels in the UTI group.

CONCLUSION

In our study, there was no relationship between vitamin D and cathelicidine in children with UTI. But in healthy children, there is a weak but positive correlation between vitamin D and cathelicidin levels. Further research using a bigger population may clarify the role of vitamin D and cathelicidin in UTIs. Additionally we think that our study will lead to other studies to determine the relationship between infections and vitamin D-cathelicidin.

Main Points

1. Cathelicidin and vitamin D levels have a positive correlation.

2. Future large-scale research may provide insight into whether cathelicidin can be used as a biomarker to support clinical findings, particularly in the differentiation of upper and lower UTIs.

REFERENCES

1. Mailhot G, White JH. Vitamin D and Immunity in Infants and Children. Nutrients 2020;12:1233.
2. Al-Khalidi B, Kimball SM, Rotondi MA, Ardern CI. Standardized serum 25-hydroxyvitamin D concentrations are inversely associated with cardiometabolic disease in U.S. adults: a cross-sectional analysis of NHANES, 2001-2010. Nutr J 2017;16:16.
3. Science M, Maguire JL, Russell ML, Smieja M, Walter SD, Loeb M. Low serum 25-hydroxyvitamin D level and risk of upper respiratory tract infection in children and adolescents. Clin Infect Dis 2013;57:392-7.
4. Riverin BD, Maguire JL, Li P. Vitamin D Supplementation for Childhood Asthma: A Systematic Review and Meta-Analysis. PLoS One 2015;10:e0136841.
5. Liu X, Arguelles L, Zhou Y, Wang G, Chen Q, Tsai HJ, et al. Longitudinal trajectory of vitamin D status from birth to early childhood in the development of food sensitization. Pediatr Res 2013;74:321-6.
6. Tekin M, Konca C, Celik V, Almis H, Kahramaner Z, Erdemir A, et al. The Association between Vitamin D Levels and Urinary Tract Infection in Children. Horm Res Paediatr 2015;83:198-203.
7. Yuk JM, Shin DM, Lee HM, CS Yang, HS Jin, KK Kim, et al. Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin. Cell Host Microbe 2009;6:231-43.
8. Li A, Zhang W, Zhang H, Yi B. Vitamin D/vitamin D receptor, autophagy and inflammation relevant diseases. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2017;42:979-85.

9. White JH. Emerging Roles of Vitamin D-Induced Antimicrobial Peptides in Antiviral Innate Immunity. Nutrients 2022;14:284.
10. Avila EE. Functions of Antimicrobial Peptides in Vertebrates. Curr Protein Pept Sci 2017;18:1098-119.
11. Weichhart T, Haidinger M, Hörl WH, Säemann MD. Current concepts of molecular defence mechanisms operative during urinary tract infection. Eur J Clin Invest 2008;38 Suppl 2:29-38.
12. Ching C, Schwartz L, Spencer JD, Becknell B. Innate immunity and urinary tract infection. Pediatr Nephrol 2020;35:1183-92.
13. Chromek M, Slamová Z, Bergman P, Kovács L, Podracká L, Ehrén I, et al. The antimicrobial peptide cathelicidin protects the urinary tract against invasive bacterial infection. Nat Med 2006;12:636-41.
14. Kai-Larsen Y, Lüthje P, Chromek M, Peters V, Wang X, Holm A, et al. Uropathogenic Escherichia coli modulates immune responses and its curli fimbriae interact with the antimicrobial peptide LL-37. PLoS Pathog 2010;6:e1001010.
15. Asadi Karam MR, Habibi M, Bouzari S. Urinary tract infection: Pathogenicity, antibiotic resistance and development of effective vaccines against Uropathogenic Escherichia coli. Mol Immunol 2019;108:56-67.
16. Balighian E, Burke M. Urinary Tract Infections in Children. Pediatr Rev 2018;39:3-12.
17. Leung AKC, Wong AHC, Leung AAM, Hon KL. Urinary Tract Infection in Children. Recent Pat Inflamm Allergy Drug Discov 2019;13:2-18.
18. Korbel L, Howell M, Spencer JD. The clinical diagnosis and management of urinary tract infections in children and adolescents. Paediatr Int Child Health 2017;37:273-9.
19. Morello W, La Scola C, Alberici I, Montini G. Acute pyelonephritis in children. Pediatr Nephrol 2016;31:1253-65.
20. Tullus K, Shaikh N. Urinary tract infections in children. Lancet 2020;395:1659-68.
21. Zhang H, Yang J, Lin L, Huo B, Dai H, He Y. Diagnostic value of serum procalcitonin for acute pyelonephritis in infants and children with urinary tract infections: an updated meta-analysis. World J Urol 2016;34:431-41.
22. Shaikh KJ, Osio VA, Leeflang MM, Shaikh N. Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children. Cochrane Database Syst Rev 2020;9:CD009185.
23. Schmidt B, Copp HL. Work-up of Pediatric Urinary Tract Infection. Urol Clin North Am 2015;42:519-26.
24. Spencer JD, Schwaderer AL, Becknell B, Watson J, Hains DS. The innate immune response during urinary tract infection and pyelonephritis. Pediatr Nephrol 2014;29:1139-49.
25. Danka ES, Hunstad DA. Cathelicidin augments epithelial receptivity and pathogenesis in experimental Escherichia coli cystitis. J Infect Dis 2015;211:1164-73.
26. Övünç Hacıhamdioğlu D, Altun D, Hacıhamdioğlu B, Çekmez F, Aydemir G, Kul M, et al. The Association between Serum 25-Hydroxy Vitamin D Level and Urine Cathelicidin in Children with a Urinary Tract Infection. J Clin Res Pediatr Endocrinol 2016;8:325-9.
27. Georgieva V, Kamolvit W, Herthelius M, Lüthje P, Brauner A, Chromek M. Association between vitamin D, antimicrobial peptides and urinary tract infection in infants and young children. Acta Paediatr 2019;108:551-6.
28. Kafle S, Basnet AK, Karki K, Thapa Magar M, Shrestha S, Yadav RS. Association of Vitamin D Deficiency With Pulmonary Tuberculosis: A Systematic Review and Meta-Analysis. Cureus 2021;13:e17883.
29. Dao CN, Patel P, Overton ET, Rhame F, Pals SL, Johnson C, et al. Low vitamin D among HIV-infected adults: prevalence of and risk factors for low vitamin D Levels in a cohort of HIV-infected adults and comparison to prevalence among adults in the US general population. Clin Infect Dis 2011;52:396-405.
30. Fujita K, Ito Y, Oguma T, Mio T, Niimi A, Hirai T. Association between Mycobacterium avium complex lung disease and serum vitamin D status, antimicrobial peptide levels, and bone mineral density. Medicine (Baltimore) 2018;97(38):e12463.
31. Thursfield RM, Naderi K, Leaver N, Rosenthal M, Alton EWFW, Bush A, et al. Children with cystic fibrosis demonstrate no respiratory immunological, infective or physiological, consequences of vitamin D deficiency. J Cyst Fibros 2018;17:657-65.
32. Serré J, Mathyssen C, Ajime TT, Korf H, Maes K, Heulens N, et al. Airway infection with Nontypeable Haemophilus influenzae is more rapidly eradicated in vitamin D deficient mice. J Steroid Biochem Mol Biol 2019;187:42-51.