ÖZGÜN ARAŞTIRMA / ORIGINAL RESEARCH

DOI: 10.17944/mkutfd.913838
MKÜ Tıp Dergisi 2022;13(45): 12-17

Could serum copeptin be used for diagnosing urinary tract infections in children?

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Abstract

Could serum copeptin be used for diagnosing urinary tract infections in children?

Objective: Early diagnosis of urinary tract infection (UTI) is important to reduce short- and long-term complications. To this end, effective biomarkers are needed. Our aim was to evaluate the role of copeptin in the diagnosis of UTI and in distinguishing upper from lower UTI compared to other inflammatory markers.
Methods: The diagnosis of UTI was based on the presence of typical clinical symptoms and a positive urine culture. The control group was formed by healthy children without signs or symptoms of infection. Complete blood count, CRP, ESR, serum IL -6, NGAL and copeptin were evaluated.
Results: The study group included 41 patients with UTI and 41 healthy controls. The patients were 5 (0.8-15) years old and 65.9% of them were female. In the patients with UTI, in addition to total WBC ($p<0.001$) and NGAL ($p=0.031$), copeptin was also increased (147.9(60.8-361.9) vs. 69.7(24.2-303) ng/ml, $p<0.001$). Copeptin could diagnose UTI at a cut-off value of 81.8 ng/ml ($p<0.001$, sensitivity 80.4%, specificity 60.5%). Within the UTI group, 10 had upper UTI and 31 had lower UTI. In the upper UTI group WBC ($p=0.019$), CRP ($p<0.001$), ESR ($p<0.001$) and NGAL ($p=0.046$) were higher. Copeptin did not differ between upper and lower UTI groups ($p=0.82$). Copeptin correlated with IL -6 and NGAL ($r^2=0.23$, $p=0.002$; $r^2=0.89$, $p<0.001$, respectively).
Conclusion: Copeptin is a useful biomarker to use in the diagnosis of childhood UTI, but more comprehensive studies are needed to evaluate its role in distinguishing upper from lower UTI.
Keywords: Copeptin, UTI, NGAL, IL-6, child

Öz

Serum copeptin çocukluk çağı idrar yolu enfeksiyonlarının tanısında kullanılabilir mi?

Amaç: Üriner sistem enfeksiyonu (ÜSE)'nin erken teşhis edilmesi kısa ve uzun dönem etkileri azaltmak için önemlidir. Bu amaçla etkili biyobelirteçlere ihtiyaç vardır. Bu çalışmada, copeptinin diğer inflamatuvar belirteçlere göre ÜSE tanısında ve alt-üst ÜSE ayırımında rolünü değerlendirmeyi amaçladık.
Yöntem: ÜSE tanısı, tipik klinik semptomlar ve pozitif idrar kültürüne dayanılarak konuldu. Kontrol grubu enfeksiyon bulgusu olmayan sağlıklı çocuklardan oluşturuldu. Hastaların tam kan sayımı, CRP, sedimentasyon, serum IL-6, NGAL ve copeptin düzeyleri değerlendirildi.
Bulgular: Çalışmaya 41'er tane ÜSE ve sağlıklı birey dahil edildi. Hastaların yaşları 5 (0.8-15) yıl olup, %65.9'u kadın idi. ÜSE'si olanlarda WBC ($p<0.001$) ve NGAL ($p=0.031$) yanında copeptin (147.9(60.8-361.9) vs. 69.7(24.2-303) ng/ml, $p<0.001$) seviyeleri anlamlı oranda yüksekti. Copeptinin 81.8 ng/ml cut-off değeri ÜSE'ye işaret etmekteydi (sensitivite %80.4, spesifite %60.5, $p<0.001$). ÜSE grubunun 10 tanesi üst, 31 tanesi de alt ÜSE tanısına sahipti. Üst ÜSE hastalarında WBC ($p=0.019$), CRP ($p<0.001$), sedimentasyon ($p<0.001$) ve NGAL ($p=0.046$) seviyeleri anlamlı oranda yüksekti. Copeptin üst ve alt ÜSE grupları arasında farklılık göstermemekteydi. Copeptin IL-6 ve NGAL ile ilişkili bulundu (sırasıyla $r^2=0.23$, $p=0.002$; $r^2=0.89$, $p<0.001$).
Sonuç: Copeptin çocukluk çağı ÜSE tanısında kullanılabilecek faydalı bir biyobelirteçtir, ancak üst ve alt ÜSE ayrımdaki rolünü değerlendirmek için daha kapsamlı çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Copeptin, İdrar Yolu Enfeksiyonu, Neutrophil Gelatinase-Associated Lipocalin, İnterlökin-6, Çocuk

Nasıl Atıf Yapmalı: Bekdaş M, Erkoçoğlu M, Karabörk Ş, Dilek M. Could serum copeptin be used for diagnosing urinary tract infections in children? MKÜ Tıp Dergisi 2022;13(45): 12-17. https://doi.org/10.17944/mkutfd.913838

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Geliş/Received: 12 Nisan 2021
Kabul/Accepted: 25 Şubat 2022

INTRODUCTION

Urinary tract infections (UTI) are an important health problem that occurs in all age groups, including childhood. UTI is more common in girls throughout life, except for the first three months of life. It has been found in 1% of boys and 1-3% of girls (1). Patients with UTI are more likely to present with nonspecific findings as they age, leading to a delay in diagnosis and treatment. Delayed diagnosis of upper UTI can lead to renal parenchymal damage in the short term and hypertension and chronic renal failure in the long term (2). Recurrent UTI and related scarring is the leading cause of chronic renal failure, especially in our country (3).

Early diagnosis and effective treatment of UTI is important to reduce the short and long-term complications. To this end, effective biomarkers are needed for both early detection of UTI and differentiation between upper and lower UTI. It has been reported that serum white blood cell (WBC) count, absolute neutrophil count (ANC), serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum IL -6 and serum NGAL can be helpful in early detection of UTI and in distinguishing upper from lower UTI (4-6). However, there is still a need for effective markers, especially to distinguish between lower and upper UTI.

Copeptin, a 39 amino acid long peptide derived from a preprohormone such as vasopressin, is a new serum marker of inflammation (7). Copeptin levels increase under conditions such as hypotension, hypoxia, acidosis, and hyperosmolality. Copeptin is synthesized along with vasopressin and its level directly reflects vasopressin (8). It plays an important role in regulating the hypothalamic-pituitary-adrenal axis, ensuring a healthy response to stressful situations (9). The increase in serum copeptin is much greater than that of vasopressin under certain conditions, and its more stable plasma concentration compared to vasopressin makes it a more useful biomarker (10,11). In conditions such as septic shock, acute myocardial infarction, and community-acquired pneumonia, elevated serum copeptin levels have been found to correlate with disease severity (10,12,13). Previously, a study in adults found that serum copeptin may be a useful biomarker for the diagnosis of UTI (14). We could not identify any study that investigated the role of copeptin in pediatric cases. In this study, we aimed to investigate the role of copeptin in the diagnosis of UTI and in distinguishing upper from lower UTI compared with other inflammatory markers.

METHODS

Patients admitted to paediatric clinics with signs and symptoms of UTI were prospectively enrolled in the study. Written informed consent was obtained from the parents.

Signs and symptoms of UTI were accepted as fever, vomiting, abdominal pain and flank pain for upper UTI; dysuria, suprapubic tenderness and pollakiuria for lower UTI. The diagnosis and classification of UTI was based on the presence of typical clinical symptoms, laboratory parameters and positive urine culture.

Urine samples were collected using a sterile plastic bag or urinary catheter in patients less than 2 years of age, and urine samples were collected from the midstream in elderly patients. A positive urine culture was defined as bacterial growth $\geq 10^3$ colony forming units (CFU)/ml in a urine sample collected with a urinary catheter and $\geq 10^4$ CFU/ml in a urine sample collected from the midstream or a sterile plastic bag (15). The control group was selected from healthy children without signs or symptoms of acute infection. All participants in the control group also had a normal urinalysis. Steroid therapy or chronic kidney disease may alter serum levels of copeptin (16,17). One exclusion criterion for this study was chronic renal failure. Another exclusion criterion was patients taking systemic steroids.

The following laboratory tests were performed on all subjects: complete blood count, CRP, ESR, renal function test, IL-6, NGAL, and copeptin. Serum samples for IL-6, NGAL and copeptin were collected and frozen at -80 °C. Copeptin, IL-6, and NGAL in serum were measured using a commercial ELISA kit (Hangzhou Eastbiopharm Co. Ltd, Hangzhou, China).

Data were analysed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variable descriptive statistics were expressed as mean±standard deviation with a normal distribution and median (min-max) with a non-normal distribution. Categorical variables were compared using the chi-square test, and continuous variables were compared using the Student-t or Mann-Whitney U test according to the normal distribution. ROC analysis was performed to determine the cut-off copeptin level at diagnosis of UTI. A p-value of less than 0.05 was considered statistically significant.

Ethical approval was obtained for this study from the Ethics Committee of Bolu Abant Izzet Baysal University of Clinical Research, and the rules of the Declaration of Helsinki were followed in the conduct of this study.

RESULTS

The study group included 41 patients with UTI and 41 healthy controls. The patients were 5 (0.8-15) years old and 14 (%34.1) of them were male. The mean age of the control group was 6 (0.2-14) years and 20 (%48.7) of them were male. WBC ($p<0.001$), serum NGAL ($p=0.031$) and serum copeptin (147.9(60.8-361.9) vs. 69.7(24.2-303) ng/ml, $p<0.001$) were significantly higher in the patient group (Table 1).

Table 1. Comparison of patients with UTI and control group

Specifications	UTI (n=41)	Control (n=41)	p
Age, mean±SD (years)*	5 (0.8-15)	6 (0.2-14)	0.093**
Sex (male, %)	34.1	48.7	0.077**
Copeptin (ng/ml)*	147.9(60.8-361.9)	69.7(24.2-303)	<0.001**
NGAL (ng/ml)*	148.1(49.6-339.6)	83.9(28.1-361.7)	0.031**
IL-6 (ng/l)*	93.4(6.5-268.6)	69.9(14.6-292.2)	0.19**
CRP (mg/l)*	5(0.1-186)	1.8(0.1-11.2)	0.06**
ESR (mm/h)*	12(2-51)	7.5(2-16)	0.065**
Total WBC (/µl)	9960±4628	6903±1710	<0.001
ANC (/µl)*	4100(700-17600)	3290(1730-7120)	0.41**
ALC (/µl)	3540±1861	2304±972	<0.001
Platelet (/µl)	309317±86132	290146±92605	0.31
MPV (fl)	7.1±1.5	7.7±1.2	0.055
Urine pH	5.6±0.9	5.4±0.7	0.27
Urine dansity	1014±8.5	1019±8.2	0.054

*:Median (Min-Max); **Mann-Whitney U; ALC: Absolute lymphocyte count; ANC:Absolute neutrophil count; CRP:C-reactive protein; ESR:Erythrocyte sedimentation rate; MPV:Mean platelet volume; NGAL: Neutrophil Gelatinase-associated Lipocalin; NLR:Neutrophil lymphocyte ratio; UTI:Urinary tract infection

After ROC analysis, we found that 81.8 ng/ml serum copeptin had the best sensitivity for predicting UTI (AUC:0.73, 95% CI (0.61-0.84), p<0.001) (sensitivity 80.4%, specificity 60.5%) (Figure1). Within the UTI group, 10 of them had an upper UTI and 31 had a lower UTI. When we compared the patients with upper and lower UTI, WBC (p=0.019), ANC (p<0.001), CRP (p<0.001), ESR (p<0.001), NGAL (p=0.046) and NLR (p < 0.001) were significantly higher in the upper UTI group. Fever was more frequent in the upper UTI group (70 vs 16.1%, p=0.01). There was no statistically significant difference in serum copeptin between upper and lower UTI patients (129(71.4-344.1) vs. 158.7(60.8-361.9) ng/ml, p=0.82) (Table 2). Copeptin correlated with IL -6 and NGAL (r^2=0.23, p=0.002; r^2=0.89, p<0.001, respectively).

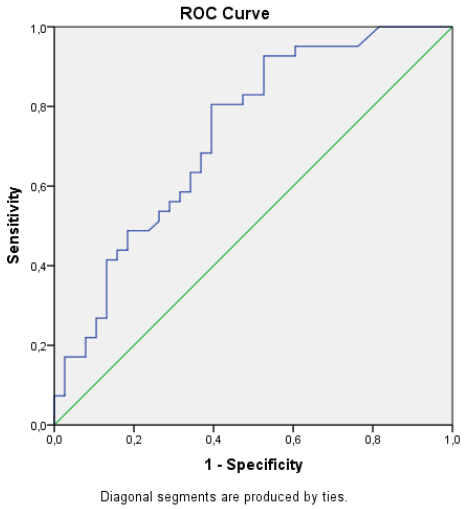

Figure 1: ROC curve analysis of serum copeptin level for discriminating UTI from control group. Cut-off:81.8 ng/ml, AUC:0.73, 95% CI (0.61-0.84), p<0.001 (Sensitivity 80.4%, Specificity 60.5%)

Table 2: Comparison of patients with upper and lower UTI

Specifications	Upper UTI (n=10)	Lower UTI (n=31)	p
Age, mean±SD (years)*	9 (0.2-12)	3 (0.8-15)	0.099**
Sex (male, %)	27.2	35.5	0.8**
Fever (%)	70	16.1	0.001**
Vomiting (%)	40	22.6	0.28**
Abdominal pain (%)	50	35.5	0.41**
Flunk pain (%)	20	3.2	0.077**
Recurrent UTI (%)	30	16.1	0.36**
Copeptin (ng/ml)*	129(71.4-344.1)	158.7(60.8-361.9)	0.82**
NGAL (ng/ml)*	256.5(49.6-339.6)	136.9(61.1-249.6)	0.046**
IL-6 (ng/l)	159.5±80.5	151.9±80	0.79
CRP (mg/l)*	77.7(19.6-186)	1.2(0.1-38)	<0.001**
ESR (mm/h)*	32(13-51)	8(2-27)	<0.001**
Total WBC (/µl)	12893±4751	9014±4242	0.019
ANC (/µl)*	11850(3500-14400)	3100(700-17600)	<0.001**
ALC (/µl)	1985±731	4041±1841	0.001
Platelet (/µl)	280000±87381	318774±84982	0.22
MPV (fl)	7±0.9	7.2±1.7	0.71
Urine pH	5.6±1	5.7±0.9	0.72
Urine dansity	1014±8.6	1013±8.5	0.95

*:Median (Min-Max); **Mann-Whitney U; ALC: Absolute lymphocyte count; ANC:Absolute neutrophil count; CRP:C-reactive protein; ESR:Erythrocyte sedimentation rate; MPV:Mean platelet volume; NGAL: Neutrophil Gelatinase-associated Lipocalin; NLR:Neutrophil lymphocyte ratio; UTI:Urinary tract infection

DISCUSSION

Depending on age, UTI may cause nonspecific signs and symptoms, leading to a delay in diagnosis. Research is being conducted to prevent this diagnostic delay, which may increase the risk of damage to the renal parenchyma. In our study, it was found that in addition to acute phase proteins, including NGAL and total WBC, serum copeptin is also higher in childhood UTI. This showed that serum copeptin level can be used as a biomarker in the diagnosis of UTI. However, serum copeptin did not differ between upper and lower UTIs.

Studies have shown that serum copeptin level can be used as a prognostic marker in the diagnosis of diseases such as community-acquired pneumonia and myocardial infarction (12,13). In addition, serum copeptin level may be a good parameter for predicting survival in septic shock (10) and post-stroke infections (18). Currently, the diagnosis UTI is made based on the presence of clinical symptoms and positive laboratory findings. Urine culture is the gold standard in UTI diagnosis, but it is both time consuming and expensive. Serum copeptin can be used as a guide for the diagnosis of childhood UTI in this case. We have shown that serum copeptin level was significantly higher in cases with UTI, which is consistent with the previous findings of Masajtis-Zagajewska et al (14). We also found that the cut-off value of 81.8 ng/ml for copeptin had the highest sensitivity for the diagnosis of UTI. These results indicate that serum copeptin can contribute to the diagnosis of UTI. In contrast to our study, the study by Masajtis-Zagajewska et al (14) was conducted in adults. The difference in cut-off values might have been caused by this reason, other reasons for this difference Masajtis-Zagajewska et al. (14) study had a higher number of upper UTI.

Our study showed that inflammatory markers such as total WBC, ANC, CRP, ESR and NLR can distinguish upper UTI from lower UTI as in previous studies (4-6). Acute phase cytokines, such as IL -6, may increase vasopressin production (19), allowing a healthy response to acute stress. In our study, IL -6 was higher in both UTI and upper UTI groups, although this was not statistically significant. On the other hand, NGAL was significantly higher in these two groups than in the literature (20). These results suggest that serum NGAL rather than serum IL -6 may be helpful in diagnosing upper UTI in patients with difficult-to-diagnose diseases. Our study showed that serum copeptin levels increased up to 2-fold in children with UTIs (147.9(60.8-361.9), vs. 69.7(24.2-303) ng/ml, $p<0.001$). Inflammation in peripheral tissues caused by stressful conditions such as infection, trauma, and surgery leads to an increase in cytokines such as IL-1, IL-6, and interferon, which increase these cytokines and are important stimulators of the hypothalamic-pituitary-adrenal axis (21). On the other hand, copeptin has been shown to play a dynamic role in increasing the release of adrenocorticotropic hormone from the anterior pituitary in concert with corticotropin-releasing hormone in stressful situations (22). In our study, we hypothesise that this is the reason for the increase in serum copeptin levels in UTI. On the other hand, this increase in serum copeptin levels in our study seems to be largely due to lower UTI. However, to distinguish upper from lower UTI, this increase is not as significant as urinary tract infection (158.7(60.8-361.9), etc. 129(71.4-344.1 ng/ml, $p=0.82$). This result showed that UTIs in children are an important trigger for serum copeptin, but this change alone does not help to distinguish the type of UTI. Nevertheless, we found a positive correlation between serum copeptin and IL -6 and NGAL.

Rechlin et al (23) found that serum copeptin levels increased in patients with myocardial infarction as early as 4 hours after the first symptom. Masajtis-Zagajewska et al (14) showed that patients with UTI still had high serum copeptin levels on the seventh day of treatment, although other acute-phase reactants normalized. We think that such a marker, which rises during stress and remains high despite treatment, can also be used to predict possible complications in these patients. However, prospective studies are needed in this regard.

The main limitations of our study are the small number of patients and the lack of long-term follow-up of patients in terms of prognosis and complications.

CONCLUSION

Serum copeptin is a useful biomarker that can be used in the diagnosis of UTI in childhood. However, more comprehensive studies are needed to evaluate its role in differentiating upper from lower urinary tract infections.

ACKNOWLEDGEMENT

Peer-Review

Externally Peer Reviewed

Conflict of Interest

The authors declare that they have no conflict of interestsregarding content of this article.

Financial Support

This study was funded by Abant Izzet Baysal University with the project number 2015.8.23.965

Ethical Declaration

Ethical permission was obtained from the Abant Izzet Baysal University, Medical Faculty Clinical / Human Research Ethics Committee for this study with date 30/12/2015 and number 2015/141, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: M.B., M.E., Design: M.B., Ş.K., Data Collection or Processing: M.E., Ş.K., Analysis or Interpretation: M.B., M.E., Literature Search: M.B., Ş.K., Writing: M.B., M.D.

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