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Obesity and risk of urinary tract infection in young children presenting with fever

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Abstract

Obesity may increase the risk of infection, but the association between obesity and febrile urinary tract infection (fUTI) is controversial. Although the prevalence of infant and childhood obesity has been increasing worldwide, the results of previous investigations on the association with urinary tract infection (UTI) are conflicting. The purpose of this study was to evaluate the relationship between overweight and obesity and UTI in febrile children.

The study reviewed medical records of a consecutive series of 472 children <2 years of age presenting with fever ≥ 38°C were retrospectively evaluated and stratified by the presence or absence of a UTI. The proportions of underweight, healthy weight, overweight, and obese children in the 2 groups were compared following calculation of individual weight-for-length percentiles. The effect of obesity on UTI risk was evaluated, and odds ratios (ORs) were calculated.

A total of 212 patients with and 260 controls without UTI were included. There were more overweight and obese children with (71/212, 33.5%) than without UTIs (45/260, 17.3%; $P < .001$). The OR of UTI in overweight relative to healthy-weight children was 1.92 [95% confidence interval (95% CI):1.15–3.21]. The OR of UTI in obese relative to healthy weight children was 2.46 (95% CI: 1.54–3.93).

Compared with previous studies that made comparison between UTI and healthy children, this is the first study to demonstrate an association of obesity and fUTI in febrile children <2 years of age. In this series of pediatric patients, obesity was strongly associated with the presence of fUTI and obese children had a higher risk of developing an UTI than nonobese children.

The incidence of UTI was higher in young, overweight, and obese children presenting with fever than in normal-weight, febrile children. Control of excess body weight should be considered as early as possible. Urinalysis should be considered for obese children <2 years of age who present with fever, especially those with mild respiratory or gastrointestinal symptoms.

Abbreviations: APN = acute pyelonephritis, CI = confidence interval, DMSA = dimercaptosuccinic acid, ED = emergency department, fUTI = febrile urinary tract infection, OR = odds ratio, SD = standard deviation, UA = urinalysis, UC = urine culture, UTI = urinary tract infection, WFL = weight-for-length.

Keywords: fever, infant/toddler, obesity, risk factors, urinary tract infections

1. Introduction

Urinary tract infections (UTIs) are a common pediatric diagnosis and may increase the risk factor of renal insufficiency or end-stage renal disease in children. UTI is estimated to present in 2.1% to 20.1% of febrile infants depending on age, sex, race, and circumcision status.[1] Clinical variables, including congenital genitourinary conditions, immature host defense, female gender, lack of circumcision, and prior history of UTI increase the risk of UTI in febrile young children.[2] Despite the high prevalence of UTI, it is difficult to diagnose in toddlers or young child who present in emergency departments (EDs) because the signs and symptoms are nonspecific, and screening is uncomfortable and time-consuming.

Childhood obesity is a complex disorder that is often accompanied by increased inflammation, altered adipokine signaling, metabolic changes, and epigenetic regulation that have clinically significant impacts on immune response.[3] Obesity may increase the risk of infection,[4] but the association between obesity and febrile UTI (fUTI) is controversial. Although the prevalence of infant and childhood obesity has been increasing worldwide, the results of previous investigations on the association with UTI are conflicting.[5–12]

The prevalence of obesity in infants and young children is increasing and its impact on UTI warrants investigation. Prompt diagnosis of UTI and its associated complications during ED visits is important. Previously published studies have been limited to UTI patients and healthy controls. Therefore, the presented study aimed to investigate the effects of overweight and obesity on the UTI in febrile children < 2 years of age, using a retrospective medical record from January 2015 to October 2016.

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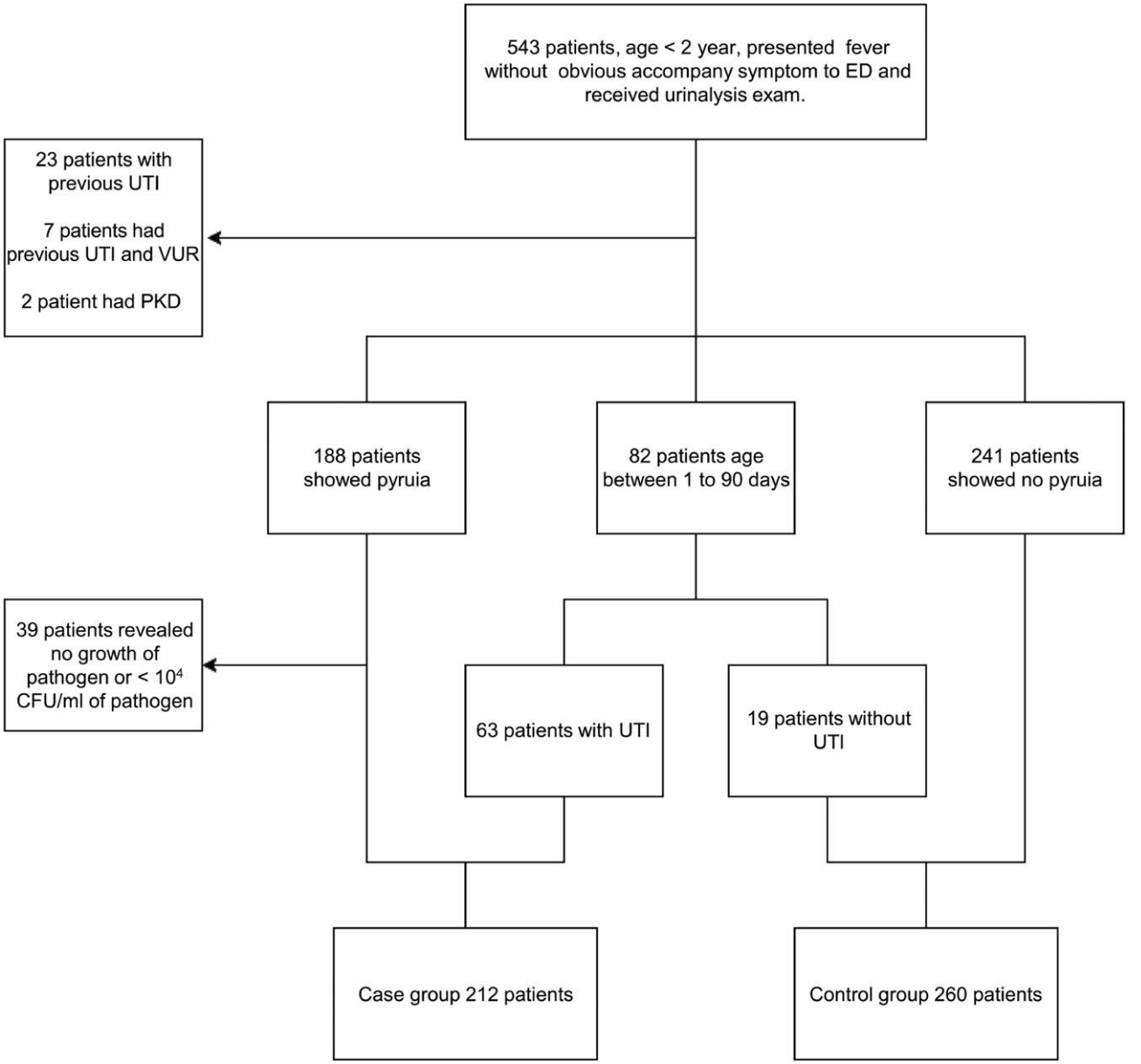

Figure 1. Flow chart of patient enrollment and exclusion. CFU = colony-forming units, ED = emergency department, UTI = urinary tract infection, VUR = vesicoureteral reflux.

2. Methods

2.1. Ethical considerations

The study was approved by the Institutional Review Board of Tri-Service General Hospital. (TSGH-IRB, approval number: 2-106-05-014). The informed consent was waived because this was a retrospective study.

2.2. Study design and patient characteristics

2.2.1. Patient*2.2.1.1. Enrollment criteria.* This retrospective study reviewed the medical records of children <2 years of age who presented at our ED between January 2015 and October 2016 with fever and had been evaluated with a urinalysis (UA). A total of 543 medical records were reviewed and 71 children were excluded (Fig. 1). Patients who was confirmed fUTI by urine culture (UC) were eligible for case group. Patients presenting with fever during the same period and without pyuria, current UTI, or a history of UTIs or renal disease were selected as controls.

2.2.1.2. Case group criteria. Eligible fUTI patients were <2 years of age. Those between 90 days and 2 years of age were eligible if they had clinical signs and symptoms, including a body temperature ≥38°C and pyuria with ≥5 white blood cells (WBCs)/high power field, and a positive UC with $\geq 10^4$ CFU/mL of a single pathogen via urinary catheterization. Children <90 days of age were eligible if they had clinical signs and symptoms, including a body temperature ≥38°C and a positive UC with $\geq 10^4$ CFU/mL of a single pathogen via urinary catheterization.

2.2.1.3. Control group criteria. Children without fUTIs were eligible if they were <2 years of age. Those between 90 days and 2 years of age were eligible if they had clinical signs and symptoms, including a body temperature ≥38°C and no pyuria, that is, <5 WBCs/high power field, on UA. Children <90 days of age were eligible if they had clinical signs and symptoms, including a body temperature ≥38°C, no pyuria, that is, <5 WBCs/high power field, and $<10^4$ CFU/mL of a single pathogen via urinary catheterization on UC.

2.2.1.4. Exclusion criteria. Patients with previous UTIs and congenital urinary tract anomalies or systemic disease were excluded from the study. Those with pyuria (>5 WBCs/high power field) but no growth or $<10^4$ CFU/mL of a single pathogen on UC were also excluded.

2.3. Categorical variables

Patients were stratified by presence of lower UTI (LUTI) or acute pyelonephritis (APN) based on the results of dimercaptosuccinic acid (DMSA) scans performed at the time of UTI diagnosis and interpreted by a nuclear medicine specialist. APN was confirmed by focal, multifocal, or diffuse decrease or absence of DMSA uptake.[13]

2.4. Obesity criteria

Body weight and height were measured, and study participants were stratified into 4 groups: underweight, healthy weight, overweight, or obese using the World Health Organization weight-for-length curves for children of the same sex and <2 years of age (Table 1), based on a recent report that identified obesity in young children.[14,15] The weight-for-length distributions of UTI patients and healthy controls were compared.

2.5. Statistical analysis

Statistical analysis was performed using SPSS 24.0 (IBM Corp., Armonk, NY). Between-group differences in categorical variables were compared with the Chi-squared test, *t* test, and Mann–Whitney *U* test. Differences in normally distributed continuous variables were compared using analysis of variance. Continuous variables that were not normally distributed were compared by the Mann–Whitney *U* test. The association of weight-for-length percentile and the occurrence of UTI was estimated by odds ratios (ORs) and 95% confidence intervals (CIs) using the fifth to 85th healthy weight percentiles the reference group. Data were reported as means ± standard deviation (SD) for continuous variables and proportions for categorical variables. Results were considered significant if $P < .05$.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the study patients are summarized in Table 1. A total of 472 patients were evaluated, 212 with (case group) and 260 without UTIs (control group). A flow chart of the patient disposition is shown in Fig. 1. The case group included 139 boys and 73 girls; the control group included 139 boys and 121 girls ($P = .005$). The fUTI patients were significantly younger (189.12 ± 154.73 days) than those without UTIs (415.58 ± 200.977 days, $P < .001$).

3.2. Weight-for-length findings

The mean weight-for-length percentile was 60.24 ± 33.66 in the case group and 55.94 ± 28.61 in the control group ($P = .003$). The case group included 14 (6.6%) underweight, 127 (59.9%) healthy weight, 29 (13.7%) overweight, and 42 (19.8%) obese children, and the corresponding values in the control group were 10 (3.8%), 205 (78.8%), 22 (8.5%), and 23 (8.8%). The between-group differences in weight-for-length percentile and frequency of obesity were significant (Table 1). Of the 212 fUTI patients, 101 had LUTIs (47.6%), 41 had APN (19.3%), and 70 did not have DMSA scan results. Four percent of the LUTI patients were underweight, 64.4% had a healthy weight, 11.9% were overweight, and 19.8% were obese. Of the APN and UTI patients without DMSA, 2.4% to 12.9% were underweight, 65.9% to 59.9% had a healthy weight, 17.1% to 13.7% were

Table 1

Clinical and demographic characteristics of controls and patients with urinary tract infection.

Variables	Controls, n (%)	UTI, n (%)	Lower UTI	APN	UTI (No DMSA)
Subjects (n)	260	212	101 (47.6%)	41 (19.3%)	70 (33.0%)
Age, d	415.58 ± 200.98	189.12 ± 154.73†	176.61 ± 149.97†	217.59 ± 141.98†	190.50 ± 167.97†
BW, kg	9.56 ± 2.58	7.23 ± 2.25†	7.12 ± 2.09†	8.11 ± 1.86†	6.85 ± 2.54†
BH, cm	75.30 ± 10.19	64.28 ± 9.18†	63.68 ± 8.72†	67.91 ± 7.24†	63.00 ± 10.34†
WFL (%)	55.94 ± 28.61	60.24 ± 33.66*	60.45 ± 32.21	61.23 ± 33.35	59.37 ± 36.26
WBC, $10^3/\mu L$		15.00 ± 6.44	15.41 ± 6.30	16.31 ± 7.04	13.65 ± 6.14
CRP, mg/dL		4.48 ± 4.64†	4.03 ± 4.36†	7.46 ± 5.32†	3.43 ± 3.95†
Gender, n (%)					
Male	139 (53.5%)	139 (65.6%)*	73 (72.3%)*	23 (56.1%)	43 (61.4%)
Female	121 (46.5%)	73 (34.4%)*	28 (27.7%)*	18 (43.9%)	27 (38.6%)
WFL category, n (%)					
Underweight	10 (3.8%)	14 (6.6%)†	4 (4.0%)*	1 (2.4%)	9 (12.9%)†
Healthy weight	205 (78.8%)	127 (59.9%)†	65 (64.4%)*	27 (65.9%)	35 (50.0%)†
Overweight	22 (8.5%)	29 (13.7%)†	12 (11.9%)*	7 (17.1%)	10 (14.3%)†
Obese	23 (8.8%)	42 (19.8%)†	20 (19.8%)*	6 (14.6%)	16 (22.9%)†

APN = acute pyelonephritis; DMSA = dimercaptosuccinic acid; LUTI = lower urinary tract infection; UTI = urinary tract infection; WFL = weight-for-length percentile.
* $P < .05$ versus controls.
† $P < .001$ versus controls.

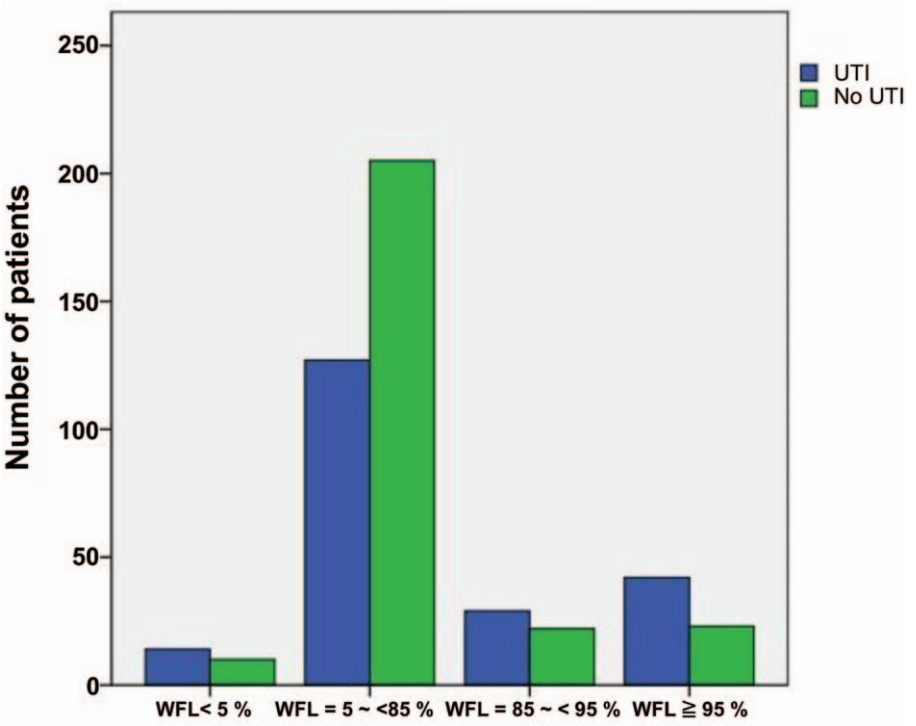

Figure 2. Weight-for-length percentile distribution in febrile patients with and without UTIs. UTI = urinary tract infection, WFL = weight-for-length percentile.

overweight, and 14.6% to 19.8% were obese. The percentage of obesity and underweight were significantly greater in UTI, and LUTI patients than in the non-UTI controls ($P < .05$, Table 1, Fig. 2).

3.3. The association of weight-for-length percentile, sex, and UTI

The ORs for UTIs differed significantly with weight-for-length percentile. The proportions of overweight, obesity, and male sex were significantly higher in fUTI patients than in the control group ($P < .001$, Table 1). Overweight and obese children were 1.92 (95% CI: 1.15–3.21; $P < .05$) and 2.46 (95% CI: 1.54–3.93; $P < .001$) times more likely than control group children to have a UTI (Table 2). Boys were 1.23 (95% CI, 1.06–1.42; $P = .005$) times more likely to have a UTI than girls, and the ORs increased with weight-for-length percentile in both boys and girls (Table 3).

4. Discussion

Obesity can increase the risk and affect the outcomes of various infectious diseases.[4] Childhood obesity is increasing, but the relationship of obesity and fUTI has not been defined. In this series of pediatric patients, obesity was strongly associated with the presence of fUTI and obese children had a higher risk of developing an UTI than nonobese children.

The results of previous studies[5–12] on the relationship of obesity and UTI are not consistent, and few have been performed in children. A cohort study of 95,598 adults found that obese patients were 2.5 times more likely to have an UTI, and nearly 5 times more likely to develop APN, and that the incidence was correlated with increasing body mass index.[5] Saliba et al[8] reported that obesity was independently associated with UTI particularly in men. However, Hirji et al [11] did not find an association of body mass index and increased risk of UTI in diabetes mellitus patients, which is in line with a study on women

Table 2

Odds ratio of the risk for urinary tract infection associated with weight-for-length percentile.

Variables	Controls	UTI		Lower UTI		APN		UTI (No DMSA)	
	n	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Subjects (n)	260	212		101		41		70	
WFL category, n (%)									
Under weight	10 (3.8%)	14 (6.6%)	2.14 (0.98–4.67)*	4 (4.0%)	1.25 (0.40–3.85)	1 (2.4%)	0.77 (0.10–5.77)	9 (12.9%)	4.40 (1.90–10.19)*
Healthy weight	205 (78.8%)	127 (59.9%)	1	65 (64.4%)	1	27 (65.9%)	1	35 (50.0%)	1
Over weight	22 (8.5%)	29 (13.7%)	1.92 (1.15–3.21)*	12 (11.9%)	1.61 (0.84–3.09)	7 (17.1%)	2.12 (0.98–4.59)	10 (14.3%)	2.29 (1.17–4.51)*
Obesity	23 (8.8%)	42 (19.8%)	2.46 (1.54–3.93)†	20 (19.8%)	2.33 (1.35–4.02)*	6 (14.6%)	1.80 (0.79–4.10)	16 (22.9%)	3.11 (1.77–5.45)†

APN = acute pyelonephritis, CI = confidence interval, DMSA = dimercaptosuccinic acid, LUTI = lower urinary tract infection, OR = odds ratio, UTI = urinary tract infection, WFL = weight-for-length.

* $P < .05$ versus controls.

† $P < .001$ versus controls.

Table 3

Odds ratio of the risk of urinary tract infection associated with gender and weight-for-length percentile.

		WFL category, n (%)								
Variables	All	OR (95% CI)	Under weight	OR (95% CI)	Healthy weight	OR (95% CI)	Over weight	OR (95% CI)	Obesity	OR (95% CI)
Male										
Controls, n (%)	139		3 (2.2%)		107 (77.0%)		15 (10.8%)		14 (10.%)	
UTI	139	1.23 (1.06–1.42)*	8 (5.8%)	3.22 (0.88–11.80)	83 (59.7%)	1	22 (15.8%)	1.70 (0.93–3.11)	26 (18.7%)	2.06 (1.14–3.74)*
LUTI	73	1.35 (1.15–1.60)*	3 (4.1%)	2.29 (0.48–10.95)	45 (61.7%)	1	10 (13.7%)	1.48 (0.71–3.08)	15 (20.5%)	2.16 (1.12–4.18)*
APN	23	1.05 (0.78–1.41)	0		14 (60.9%)	1	6 (26.1%)	2.44 (1.07–5.54)*	3 (13.0%)	1.53 (0.49–4.76)
UTI (No DMSA)	43	1.15 (0.92–1.43)	5 (11.6%)	6.32 (1.60–24.92)*	24 (55.8%)	1	6 (14.0%)	1.63 (0.69–3.84)	8 (18.6%)	2.16 (0.99–4.70)
Female										
Controls, n (%)	121		7 (5.8%)		98 (81.0%)		7 (5.8%)		9 (7.4%)	
UTI	73	0.74 (0.59–0.93)*	6 (8.2%)	1.8 (0.64–5.08)	44 (60.3%)	1	7 (9.6%)	2.06 (0.76–5.56)	16 (21.9%)	3.17 (1.49–6.73)
LUTI	28	0.60 (0.42–0.84)*	1 (3.6%)	0.71 (0.09–5.51)	20 (71.4%)	1	2 (7.1%)	1.36 (0.30–6.13)	5 (17.9%)	2.38 (0.87–6.48)
APN	18	0.94 (0.65–1.37)	1 (5.6%)	1.07 (0.14–8.08)	13 (72.2%)	1	1 (5.6%)	1.07 (0.14–8.08)	3 (16.6%)	2.23 (0.67–7.37)
UTI (No DMSA)	27	0.83 (0.60–1.15)	4 (14.8%)	4 (1.33–12.05)*	11 (40.8%)	1	4 (14.8%)	4 (1.33–12.05)*	8 (29.6%)	5.01 (2.21–11.34)*

APN = acute pyelonephritis, CI = confidence interval, DMSA = dimercaptosuccinic acid, LUTI = lower urinary tract infection, OR = odds ratio, UTI = urinary tract infection, WFL = weight-for-length.

* $P < .05$ versus controls.

† $P < .001$ versus controls.

with diabetes and UTIs,[12] and in a recent series hospital series presenting with UTIs.[10] Few studies evaluated the effects of obesity on UTIs in children. Yang et al[6] reported that obesity was a risk factor for UTI and APN in children younger than 3 years of age. Mahyar et al,[9] finding a significant association of overweight and obesity with UTI, concluded that overweight and obesity may be involved in the pathogenesis of UTI in children, and a cohort study of 86,638 children found that obesity increased the risk of UTI by 45% in girls but had no influence on the risk in obese boys.[7]

A recent study reported an association of increased ED visits for pediatric UTIs and the prevalence of obesity.[2] An association of obesity and UTI implies changes in immune function, with potential development of chronic low-grade systemic inflammation, changes in the complex interactions of adipokines, immune cells and cellular metabolism, and epigenetic changes that influence immune function.[3,4] As obesity disturbs the normal interaction of adipocytes and immune cells, it may lead to dysregulation of immune responses and increased risk of infection. An association of obesity and sympathetic hyperactivity may also contribute to development of UTIs by disturbing the normal balance of sympathetic and parasympathetic activity controlling voiding and urine storage.[16,17]

All the patients included in this study were <2 years of age, had presented at the ED with fever, and their evaluation included UA. Previous studies have estimated an overall prevalence of UTI of approximately 7% in febrile infants and young children[1,18] and 3.9% in young children presenting at EDs with fever.[19] In this study, which evaluated patients <3 months of age, the reliability of UA may be questionable. The American Academy of Pediatrics guidelines[20] recommend that the diagnosis of UTI includes an abnormal UA in addition to a positive UC, but these guidelines do not apply to infants <2 months of age. Traditional dogma holds that UA cannot be trusted in young children and previous studies[21–23] have questioned the reliability of UA in febrile young children. However, Bachur et al reported that UA had a sensitivity of 82% and that it did not decrease in children <2 years of age.[21] In a study of 770 infants with UTI who were <90 days of age, the reported sensitivity of UA combined with dipstick and microscopic analysis was about 95%.[22] However, if UTI was defined as pyuria and/or detectable leukocyte esterase, then the sensitivity (99.5%) and specificity (87.8%) were higher than seen with pyuria alone (98.3% and 63.5%, respectively).[23] At our institution, as in many others, infants <90 days of age with fever routinely undergo laboratory evaluation, including UA, UC, and blood culture for bacterial infection. They are admitted and treated with antibiotics regardless of the screening test results. In this study, patients <90 days of age with negative UA and a positive UC were assigned to and evaluated in the UTI group. They were included in the group without UTI if both the UA and UC were negative. We believe that this evaluation minimized the risk of misdiagnosis of infant UTI. The study results support previous observations that obesity was strongly associated with the presence of UTI and APN in the febrile children presenting at EDs. Despite differences in clinical practice or setting, we recommend that UTI be included in the differential diagnosis of all obese febrile children seen in the ED. In addition, we believe that our finding demonstrates useful information for further large-scale prospective cohort studies on pediatric obesity, and point out the importance of preventing obesity for both clinicians and health care payers.

The main limitations of this study were its retrospective design, which depended on data from the electronic medical records of a small number of patients. Prospective studies including larger participant populations are required to corroborate these findings. Circumcision status is another variable that may contribute to UTI.[1,2,18,19,23,24] Given the age of our patient series, an uncircumcised status and impaired immunity could have had a synergistic effect in obese patients. However, infants are not routinely circumcised in this country. Finally, 70 of the 212 UTI patients did not receive a DMSA scan, and may have reduced the incidence of APN. However, concerns of radiation exposure, and following American Academy of Pediatrics guidelines,[20] DMSA is not currently used to evaluate children with an initial UTI.

5. Conclusion

To the best of our knowledge, this is the first study to demonstrating an association of obesity and fUTI in febrile children <2 years of age. The incidence of UTI was higher in young, overweight, and obese children presenting with fever than

in normal-weight, febrile children. The findings suggest that obesity may be a predisposing factor and that control of body weight early in life in children with UTI may help prevent future chronic kidney disease. UA should be considered in the evaluation of obese febrile children <2 years of age, especially those presenting with mild respiratory or gastrointestinal symptoms.

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