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Research Article

Blood Urea Nitrogen, Serum Creatinine and Blood Urea Nitrogen to Creatinine Ratio Reference Values in Iranian Children

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ABSTRACT

Background and objectives: Reference values of blood urea nitrogen (BUN), serum creatinine (sCr) and BUN to creatinine ratio (BCR) in the different pediatric populations are not well-established yet. The aim of this study was to determine reference values of BUN, sC and BCR in healthy Iranian children.

Methods: The study included 3268 children (1670 males and 1598 females) who were hospitalized at Ali-Asghar Children's Hospital (Tehran, Iran) between April 2016 and May 2018. The subjects were stratified into three age groups: toddlers, developing children and adolescents. Demographic data, medical history and laboratory findings were extracted from medical records of the subjects. Statiscal analyses were peformed using SPSS at statistical significance of 0.05.

Results: The mean (95th Percentile) level of BUN was 12.60 mg/dl (range: 6.8 to 20.5 mg/dl). The mean and 95th percentile of sCr was 0.77 mg/dl (range: 0.8 to 1.15 mg/dl). The mean and 95th percentile of BCR was 16 (range: 12.75 to 15.4). The BUN, sCr and BCR levels differed significantly between males and females ($P<0.05$). In both genders, the concentrations of BUN and sCr were significantly higher in older children ($P<0.05$). On the contrary, the BCR value decreased significantly with age in both males and females ($P<0.05$).

Conclusion: This study is the first to report the BUN, sCr, and BCR reference values among healthy Iranian children. These values can be used by clinicians for diagnostic and therapeutic purposes.

Keywords: Blood urea nitrogen; creatinine; children; Iran

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INTRODUCTION

Blood urea nitrogen (BUN) is a clinical test to measure the amount of urea nitrogen in the blood. Urea is a product of protein metabolism in the liver. In fact, BUN is a non-protein nitrogenous (NPN) waste product of amino acids that is converted to urea by liver enzymes and later excreted by the renal system. However, the concentration of urea is dependent on protein intake (1,2). BUN is an indicator of renal function and ranges between 2.1 and 7.1 mmol/L or 6 and 20 mg/dL in adults. However, the reference ranges may differ between laboratories depending on the assay methods. BUN is influenced by various factors such as protein diet, variables in protein synthesis, the patient's hydration status and renal function status. The level of BUN is not a suitable marker for renal clearance (3). Frequently, BUN is measured using the uricase and glutamate dehydrogenase methods that both measure ammonium (4).

Creatine is generally synthesized in the liver, pancreas, and kidneys. The produced creatine in then phosphorylated and converted to phosphocreatine in the skeletal muscle and brain. About 2% of creatine is converted to creatinine every day. Creatinine is a NPN byproduct of creatine breakdown (5). The kidneys filter out most of the creatinine in urine. Elevated creatinine levels could suggest kidney dysfunction. Some temporary factors may cause a slightly higher serum creatinine (sCr) and BUN level. Persistently high level of sCr and BUN can result in severe kidney damage (6). The sCr test be performed either chemically or enzymatically. The Jaffe reaction is a chemical method that is non-specific for measuring creatinine because it can be influenced by the presence of ascorbic acid, acetone and cephalosporins erroring the samples. Moreover, the chemical method is time-consuming and not commonly used in automated analyzers (5). In addition, sCr can be measured enzymatically by assessing the activity of creatininase. It is well-demonstrated that the BUN/plasma creatinine ratio (BCR) provides a more accurate estimation of kidney function (6,7). Given the importance of determining reference values of BUN and sCr in different countries, we conducted this study using a comprehensive database to introduce BUN, sCr and BCR reference values in Iranian children.

MATERIALS AND METHODS

This retrospective study was conducted on 3268 children who were hospitalized at Ali-Asghar Children's Hospital affiliated to Iran University of medical science (Tehran, Iran) between April 2016 and May 2018. The subjects were divided into three age groups: toddlers, developing children and adolescents. Those without a history of kidney or urinary tract diseases or candidates for tonsillectomy, circumcise, herniotomy and hirschsprung disease were considered as healthy children. A history of chronic diseases such as diabetic mellitus, hepatic diseases and renal diseases as well as consumption of medications known to affect the liver or kidneys were considered as the exclusion criteria. A well-designed questionnaire was prepared to collected demographic data, medical history, cause of admission and clinical laboratory findings such as BUN and sCr.

According to the hospital protocols for BUN and sCr testing, non-fasting blood samples (5 ml) were taken in the morning in a sitting position. Measurement of BUN and sCr were carried out using the Cobas Integra® 400 plus automated analyzer (Roche Diagnostics, Mannheim, Germany). Calibrator for automated systems (C.f.a.s) was used. Quality assurance/quality control was done to ensure the accuracy and precision of the test results. Quality control was performed as defined in the test specification for every analysis (8-11). The BCR value was calculated manually. The

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study was approved by the Ethics Committee of the hospital. All personal information remained confidential throughout the study.

For data analysis, the mean and 95th percentile average of BUN, sCr and BCR were used. The Pearson's correlation coefficient was used to evaluate correlations between the parameters. Comparison of BUN, sCr and BCR values between males and females was carried out using the Mann–Whitney U test. All statistical analyses were performed using SPSS 16.0 statistical software package (SPSS, Chicago, IL, USA) or Graph Pad Prism (Graph Pad Software Inc., San Diego, CA) at significance of 0.05.

RESULTS

A total number of 3268 children were included in the study. There were 1670 (51.1%) males and 1598 (48.9%) females. The mean ± standard deviation (SD) of BUN reference value was 12.60±2.20 mg/dl. This value was 13.08±2.10 mg/dl for males and 12.11±2.31 mg/dl for females. The ninety-fifth percentile for BUN was 6.8 to 20.5 mg/dl for the study population (Table 1).

Table 1. Reference value of BUN (mg/dl) according to age and gender

Gender	Age (years)	Numbers	95% Reference intervals	Max value (mg/dl)	Min value (mg/dl)	Median (mg/dl)	Mean±SD (mg/dl)
Male	1-5	625	0.60-1.10	22	7.5	14.75	13.08±2.10
	6-10	536	0.50-1.00	20	7	13.5	
	11-15	509	0.50-1.10	19	6	12.5	
	1-15	1670	0.60-1.20	20.5	6.8	13.6	
Female	1-5	561	0.50-1.10	20	7	13.5	12.11±2.31
	6-10	486	0.50-1.00	19	6	12.5	
	11-15	551	0.50-1.10	18	5	11.5	
	1-15	1598	0.60-1.10	19	6	12.5	
Total		3268	0.60-1.20	20.5	6.8	13.65	12.60±2.20

The mean reference value of sCr was 0.77±0.05 mg/dl. This value was 0.83±0.05 mg/dl for males and 0.76±0.05 mg/dl for females. The ninety-fifth percentile for BUN was 1.15 to 8 mg/dl for the study population (Table 2).

Table 2. Reference value of sCr (mg/dl) according to age and gender

Gender	Age (years)	Numbers	95% Reference intervals	Max value (mg/dl)	Min value (mg/dl)	Median (mg/dl)	Mean±SD (mg/dl)
Male	1-5	625	0.60-1.10	1.1	0.5	0.8	0.83±0.05
	6-10	536	0.50-1.10	1.2	0.6	0.9	
	11-15	509	0.50-1.00	1.3	0.7	1.0	
	1-15	1670	0.60-1.20	1.2	0.6	0.9	
Female	1-5	561	0.60-1.10	0.9	0.4	0.7	0.76±0.05
	6-10	486	0.50-1.00	1.1	0.5	0.8	
	11-15	551	0.50-1.00	1.2	0.6	0.9	
	1-15	1598	0.60-1.20	1.0	0.5	0.8	
Total		3268	0.60-1.20	1.15	0.8	1.0	0.77±0.05

The mean reference value of BCR was 16.90±5.0. This value was 17.67±5.32 for males and 16.08±4.66 for females. The ninety-fifth percentile for BUN was 12.75 to 18 for the study population (Table 3).

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Table 3. Reference value of BCR according to age and gender

Gender	Age (years)	Numbers	95% Reference intervals	Max value (mg/dl)	Min value (mg/dl)	Median (mg/dl)	Mean±SD (mg/dl)
Male	1-5	625	0.60-1.20	24.5	19	21.75	17.67±5.32
	6-10	536	0.50-1.10	15.5	11.5	13.5	
	11-15	509	0.50-1.00	14.5	8.5	11.5	
	1-15	1670	0.60-1.20	18.17	13	15.6	
Female	1-5	561	0.60-1.10	22	17.5	19.75	16.08±4.66
	6-10	486	0.50-1.00	15	12	13.5	
	11-15	551	0.50-1.10	15	8	11.5	
	1-15	1598	0.60-1.20	17.4	12.5	14.9	
Total		3268	0.50-1.20	18	12.75	15.4	16.90±5.0

There BUN, sCr and BCR values differed significantly between males and females (Figures 1-3). As shown in figure 1, in both genders, BUN increased significantly with age (males=P<0.04, females= P<0.03).

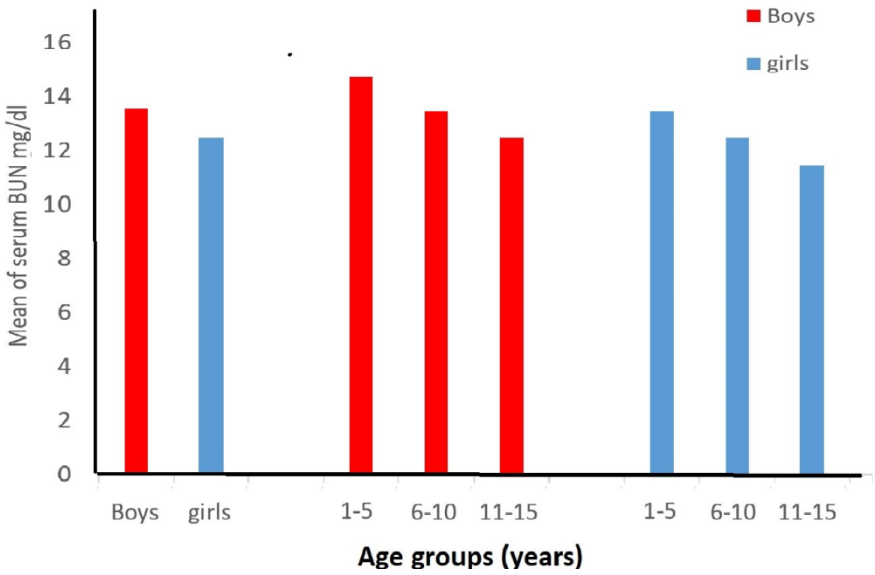

Figure 1. Comparison of BUN values according to age groups and gender.

Based on the results, sCr increased significantly with age in both males (P<0.05) and females (P<0.03) (Figure 2).

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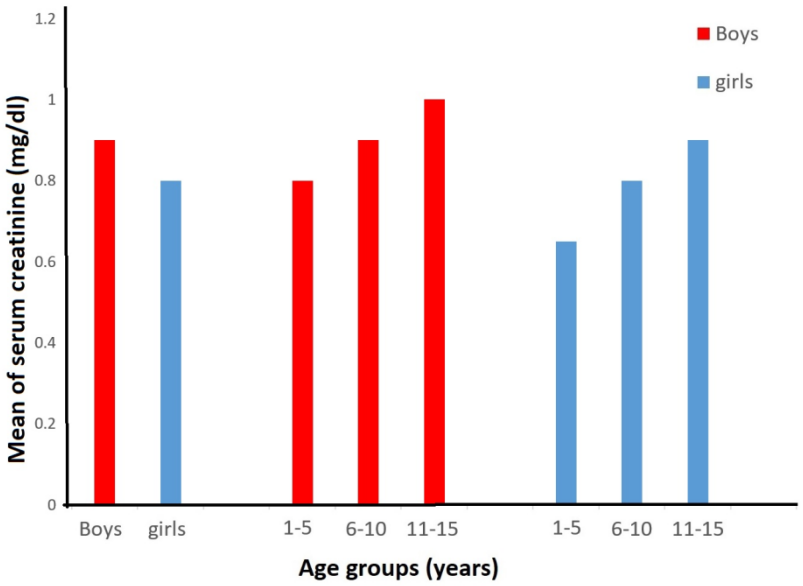

Figure 2. Comparison of sCr values according to age groups and gender.

Moreover, BUN and sCr were significantly higher in males than in females (P<0.05). As shown in figure 3, BCR decreased significantly with age in both males and females (P<0.04). In fact, there was a significant negative correlation between BCR and age in the study population.

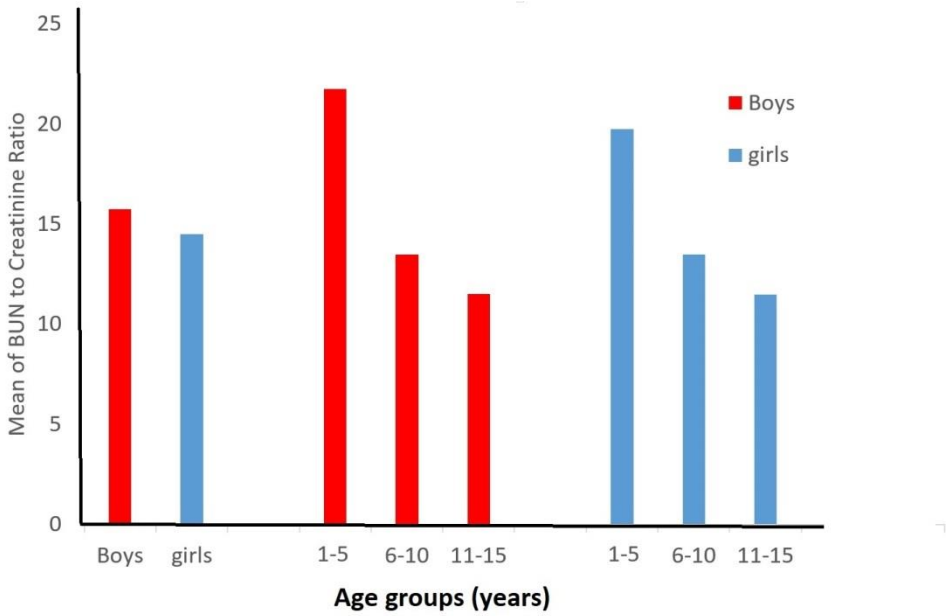

Figure 3. Comparison of BCR values according to age groups and gender.

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DISCUSSION

Reference values should be established whenever a new test is introduced or an existing method is changed. The National Committee for Clinical Laboratory Standards (NCCLS) recommends testing at least 120 samples for the establishment of a statistically significant reference interval. Other experts recommend a minimum of 200 samples to ensure stable lower and upper reference limits (12). In the present study, pre-analytical factors such as the timing of collection, consumption of food and water and medication 24 hours before testing, venipuncture site, tourniquet time and type of sample collection tube were controlled to ensure that accurate reference values are derived. This study is the first to establish reference values of BUN, sCr and BCR for healthy children aged 1-15 years in Iran. Each age group had a minimum of 486 subjects that is required for 95% reference interval determination as recommended by the NCCLS (12). However, the rate of urea production is elevated in those with a high protein diet and conditions characterized by enhanced tissue breakdown such as massive bleeding, trauma, glucocorticoid therapy and some antibiotic therapies. It is known that a low-protein diet or liver disease can decrease the BUN level without affecting glomerular filtration rate or renal function. Our study showed that the reference value of sCr concentration was age- and gender-dependent among the Iranian children. Our study showed that boys had significantly higher BUN concentrations compared to girls. Another study reported that the value of sCr is sex-related after the age of 14 years and increases steadily towards the adult levels (13). In our study, the sCr value in subjects $\geqslant$11 years was similar to that in the adult population. The sCr levels were significantly higher in males than in female subjects. It has been well-demonstrated that sCr values generally increase with age during sexual maturation. The sCr value can range from 0.5 to 1.0 mg/dL, according to the diurnal and menstrual variations, race, diet and even method of meat preparation (14,15). Furthermore, intense exercise can increase creatinine levels by increasing muscle breakdown (16,17). Jones et al. also reported that the higher sCr level in men compared with women for each age group might be attributed to the greater muscle mass in men (18). Ghasemi et al. reported that concentrations of sCr are gender-dependent in Iranian children and ranging between 1.20 to 6.0 mg/dl and 1.00 to 6.0 mg/dl in Iranian boys and girls, respectively (19). In a previous study, children had significantly lower sCr and BUN values than adults. In our study, sCr and BUN values were significantly higher in males than in females, while the concentrations of sCr increased with age. On the contrary, the BCR value decreased with age, which is consistent with a previous report (20). On the contrary, Burritt et al. reported higher BUN levels in children compared with adults (15). Hristova and Henry reported a reference interval of 10-20 for the BCR; although, for most individuals, BCR ranged between 12 and 16.5. High BCR with normal sCr levels are typically associated with high protein intake. A low BCR could reflect low protein intake in patients with severe liver disease, but this is extremely rare (21). In our study, the maximum reference value of BCR in children was lower than the maximum reference value in adults. This could be due to a high protein intake in the study population. Another study also stated that higher BUN and sCr reference values in children may be due to an unusually high protein intake (22). However, geographic and lifestyle factors may also influence these values (23,24). The reference values obtained in our study are similar to those obtained for Spanish children (14).

CONCLUSION

This study is the first to establish reference

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values for BUN, sCr and BCR among healthy Iranian children. We have defined age-specific reference values to guide the evaluation of kidney function and hydration status in healthy Iranian children. Moreover, these findings can be beneficial for renal disease examination and therapeutic procedures.

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DECLARATIONS

Funding

Not applicable.

Ethics approvals and consent to participate

This study was approved by the Local Ethical Committee of Ali-Asghar Children's Hospital, Tehran, Iran. All personal remained confidential throughout the study.

Conflict of interest

The authors declare that there is no conflict of interest.

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