

Original Article

The association between Sodium Urinary Discharge (FENa) and growth parameters in pediatrics with cystic fibrosis

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Abstract: Background: Given the association between chronic sodium losses and growth parameters and establishment of normal weight gain and linear growth in patients with cystic fibrosis (CF), in this study, we aimed to evaluate the sodium status in Iranian CF patients and its association with their growth parameters. Methods: In this prospective cross-sectional study, 44 children with CF were included. Serum and urinary sodium and creatinine levels were measured in patients, and the fractional excretion of sodium was calculated. The patients categorized in groups with FENa <0.5%, between 0.5% and 1.5% and >1.5%. Growth parameters were compared in the group, and its association with FENa level was evaluated. Results: In this study, 44 (27 boys and 17 girls) children with CF were included. Mean age of the studied population was 55.63 (33.2) months. In the studied patients with CF, 90.9% had a z score of -2_+2 (normal range) for BMI, 72.7% for weight, and 70% for height. From children with CF, 18 (40.9%) had FENa less than 0.5, 17 (38.6%) had FENa between 0.5-1.5, and 9 had FENa >1.5. From studied patients with CF, 16 (88.9%) had normal serum Na levels, but the FENa was ≤ 0.5 . Based on the Spearman correlation test, there was not any significant correlation between FENa classification and the Z score of weight (P=0.92), height (P=0.83), and BMI (P=0.99). Conclusion: Our findings indicated that most patients with a low level of FENa had normal serum sodium levels. We did not find a significant association between FENa and growth parameters. The association had a trend to be significant for BMI. It is suggested that it may be due to appropriate follow-up of the studied population. However, it is recommended to plan more studies by including healthy subjects to obtain results that are more accurate.

Keywords: Cystic fibrosis, height, weight, body mass index, fractional sodium excretion

Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder common to all races [1]. The disease is caused by a genetic mutation in the CFTR gene that leads to a reduced amount of CFTR protein and increases the activity of sodium channels in airway epithelial cells [2], which gradually leads to pulmonary dehydration and ciliary dysfunction. Primary problems in CF patients are chronic obstruction and recurrent infections in the respiratory system, as well as digestive system disorders [3].

CF patients are at risk for enhanced sodium loss due to chloride channel dysfunction, followed by loss of sodium from the skin and digestive system [3]. While in hot countries, this

can result in apparent hyponatremia in up to 95% of CF patients [4, 5], serum sodium concentrations in areas with moderate climates may remain normal despite the patients have a vital sodium depletion [4]. The situation is named after "Normonatremic sodium depletion" (NNaD), and may not be recognized if sodium concentrations are measured only in blood [6]. NNaD often reveals with only nonspecific manifestations such as unwell feeling, sleeplessness, chronic fatigue, decreased blood pressure, and anorexia [7]. Improving sodium status was demonstrated to restore normal weight gain and linear growth [4]. It thus appears that early finding of sodium depletion in CF patients is very important to control the imminent consequences in the future [8]. Given the limited ability of measuring serum or urine sodium to indi-

cate the total sodium status of patients, it seems that calculation of the fractional excretion of sodium which indicates the percentage of filtered sodium excreted in the urine is a more valid criterion, better than measurement of serum sodium or urine sodium concentrations alone [9, 10].

FENa values below 0.5% have been shown to be a valid benchmark for low sodium balance in the body and have provided an acceptable indicator for reducing total body sodium levels [4, 9, 10].

Iranian CF patients currently are managed based on American guidelines of Cystic Fibrosis Foundation, and NaCl supplement is taken by the patients according to these guidelines. Given that the climate in our region is different than the USA and in order to develop a new local clinical guideline for Iranian CF patients and also considering the association between chronic sodium losses and growth parameters and establishment of normal weight gain and linear growth in patients with cystic fibrosis (CF), in this study, we aimed to evaluate the sodium status in Iranian CF patients and its association with their growth parameters.

Methods and material

Study design

In this prospective cross-sectional study, forty children diagnosed with cystic fibrosis visiting Imam Hossein Children's Hospital from 2017 till 2019. The study was approved by the ethics committee of the Isfahan University of Medical sciences with a research project number of 398375 and ethics code of IR.MUI.MED.REC.1398.375. It should be noted that the informed consent was signed by the parents of all included children.

Inclusion and exclusion criteria

Inclusion criteria: previously diagnosed CF children who had not acute infections, inflammatory diseases, renal failure, diabetes mellitus, SIADH, cardiac failure or liver failure, and no prescriptions for diuretics. Those participants who failed to take oral NaCl, regularly visit the hospital, were reluctant to cooperate in the study were excluded from the study.

Data collection

Patients were visited every three months at the Children's CF Clinic for periodic examinations. A questionnaire was designed based on studied factors. Serum and urinary sodium and creatinine levels were measured in patients, and the data was recorded in a chart periodically. The fractional excretion of sodium, i.e., $FENa = \frac{\text{urinary Na} \times \text{plasma creatinine} \times 100}{[\text{plasma Na} \times \text{urinary creatinine}]}$ (with all parameters expressed in mmol/L), was calculated.

The FENa was calculated and sorted in predetermined tables in the format of serum sodium <135, 135-145 and >145, FENa <0.5%, 0.5%-1.5% and >1.5%. The patients were compared in terms of treatment efficacy based on sodium level (135-145) and acceptable FENa level (0.5%-1.5%).

Statistical analysis

All information was recorded in the data collection form, and statistical analyses were performed using IBM SPSS statistics software version 22. Numerical data were reported as mean (SD) and non-numerical data as number (percentage). An independent t-test was used to compare quantitative data between the two genders. The Chi-Square test was used to compare qualitative data between the two genders. A *p*-value of <0.05 was considered statistically significant. A Spearman correlation test was performed to determine the relationship between FENa values and the weight, height, and BMI Z scores in studied population variables.

Results

Patient's data

In this study, 44 (27 boys and 17 girls) children with CF were included. The mean age of the studied population was 55.63 (33.2) months. 90.9% of the patients had Z score of -2 to +2 (normal range) for BMI, 72.7% for weight and 70% for height.

A Z-score is a numerical measurement that describes a value's relationship to the mean of a group of values. Z-score is measured in terms of standard deviations from the mean. If a Z-score is 0, it indicates that the data point's score is identical to the mean score.

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Table 1. Characteristics of CF patients with FENa ≤ 0.5 , $0.5 < \text{FENa} < 1.5$ and ≥ 1.5

Variables	CF patients with FENa ≤ 0.5 n=18	CF patients with $0.5 < \text{FENa} < 1.5$ n=17	CF patients with FENa ≥ 1.5 n=9	P value
Demographic				
Age (months)	56.00 (33.01)	61.29 (36.80)	44.22 (26.17)	0.46
Sex (female/male)	6/12	9/8	9/7	0.25
Anthropometric				
Mean z-score for Weight for age	-1.44 (0.88)	-1.75 (1.18)	-1.67 (1.38)	0.49
Z score category for weight [n (%)]				
Weight Z score ≤ -2	4 (22.2%)	7 (41.2%)	1 (11.1%)	0.21
$-2 < \text{Weight Z score} \leq 2$	14 (77.8%)	1 (58.8%)	8 (88.9%)	
Weight Z score > 2	0 (0%)	0 (0%)	0 (0%)	
Mean z-score for Height for age	-1.67 (1.33)	-2.06 (1.52)	-1.33 (1.66)	0.47
Z score category for Height				
Height Z score ≤ -2	3 (16.7%)	7 (41.2%)	3 (33.3)	0.27
$-2 < \text{Height Z score} \leq 2$	15 (83.3%)	1 (58.8%)	6 (66.7%)	
Height Z score > 2	0 (0%)	0 (0%)	0 (0%)	
Body mass index (BMI) (kg/m ²)	14.78 (1.93)	14.82 (1.47)	15.11 (1.96)	0.89
Z score category for BMI				
BMI Z score ≤ -2	1 (5.6%)	1 (5.9%)	0 (0%)	0.69
$-2 < \text{BMI Z score} \leq 2$	16 (88.9%)	16 (94.1)	8 (88.9%)	
BMI Z score > 2	1 (5.6%)	0 (0%)	1 (11.1%)	
Mean z-score for BMI for age	-0.89 (1.37)	-0.76 (1.15)	-0.78 (1.48)	0.96
Biochemical				
Urine Na (mmol/L)	72.06 (50.72)	159.71 (54.36)	152.45 (54.88)	< 0.001
Plasma Na (mmol/L)	136.89 (2.49)	139.06 (2.49)	136.89 (3.40)	0.04
Urine Creatinine (mmol/L)	82.06 (33.77)	89.24 (30.17)	24.56 (13.34)	< 0.001
Plasma Creatinine (mmol/L)	0.33 (0.48)	0.41 (0.50)	0.22 (0.44)	0.64
Plasma Na [n (%)]				
< 135 mmol/L	2 (11.1%)	0 (0%)	1 (11.1)	0.36
$-135 \leq \text{Na} < 145$	16 (88.9%)	17 (100%)	8 (88.9%)	

FENa evaluations

From children with CF, 18 (40.9%) had FENa less than 0.5, 17 (38.6%) had FENa between 0.5-1.5 and 9 had FENa > 1.5 . Characteristics of patients with FENa ≤ 0.5 , $0.5 < \text{FENa} < 1.5$ and ≥ 1.5 are presented in **Table 1**. Studied patients in the three group was similar regarding their age, sex and anthropometrics variables ($P > 0.05$).

Further measurements

The mean of urine Na was significantly higher in patients with FENa > 0.5 ($P < 0.001$).

The mean of serum Na level was significantly higher in patients with $0.5 < \text{FENa} < 1.5$ than in the two other groups ($P = 0.04$). The mean of urine creatinine was significantly lower in pa-

tients with FENa ≥ 1.5 ($P < 0.001$). From studied patients with CF, 16 (88.9%) had normal serum Na levels, but the FENa was ≤ 0.5 .

Based on the Spearman correlation test, there was not any significant correlation between FENa classification and the Z score of weight ($P = 0.92$), height ($P = 0.83$), and BMI ($P = 0.99$).

Discussion

This study evaluated the proportion of CF patients with a low level of FENa and its association with anthropometric variables Z score. Our findings indicated that 41% of the studied CF patients had FENa less than 0.5. In patients with low FENa levels 88.9% had normal serum Na levels. There was no significant association between FENa and growth parameters.

Given that sodium depletion may be associated with failure to thrive specially in patients with chronic diseases such as CF, and the importance of proper growth in the outcome of CF in affected patients, this study was conducted [11].

Recently, keivanfar and colleagues in our region have demonstrated that using of plasma sodium had higher sensitivity than FENa, and FENa had higher specificity than plasma sodium to follow up of patients with CF [12].

Many studies have reported the rate of growth failure (less than the 10th percentile of weight and height-for-age) in children with CF. Findings of a cohort study indicated that 23.9% of infants with CF were below the 10th percentile of length for age, and 13.6% were below the 10th percentile of weight-for-age at one year of age [13]. Based on the CF Foundation registry report, 54% of CF patients were at the goal of 50th percentile for BMI [14].

Based on available data, the proportion of patients with low BMI are higher than that reported for height and weight. It may be due to that BMI calculation is related inversely with height, and some studies indicated that the proportion of height for age less than the 10th percentile is higher than the proportion related to weight [15, 16]. Evidences indicated that in CF patients with BMI percentile of 25-50, the rate of weight and height for age below the 10th percentile were 16.8% and 26.6%, respectively [17].

Konstan and colleagues demonstrated that BMI fails to identify a substantial proportion of children with CF who have stunting or potentially poor nutritional status measured by WFA and/or HFA. To avoid possible BMI-based misconceptions that children have good nutritional status, both WFA and HFA percentiles should be closely monitored in routine clinical practice [17].

In the current study, 30% of patients with CF had a Z score less than -2 for weight and height, and 10% had Z score below -2 for BMI.

Considering that we have no CF screening in our region, the proportion of weight and height below the 10th percentile of age in our study

was higher than that reported for children during the early year of life.

Knepper and colleagues evaluated the relationship between FENa and growth in CF children. Based on their results, 71.4% of their studied population had FENa less than 0.5. They studied patients aged more than two years [4].

The rate in our study was 41%; this was to be expected because Iranians consume more salt than the global average in their diet [18, 19]. We had no age limitation for patients' selection, whereas they included patients with CF who aged more than two years. The differences between our results and that reported by Knepper and colleagues [4] may be due to the included patients without any age limitation or our treatment protocol for CF patients Or more salt use in the Iranian diet.

In our study, 88.9% of patients with a low level of FENa had normal plasma Na levels, and in the study of Knepper and colleagues [4], 100% of the patients with low FENa had normal plasma sodium level. Our findings in this regard were similar to those reported by the mentioned study.

In the study of Knepper and colleagues [4, 20] among 35 children with CF, there was a significant association between FENa and z-scores for weight ($r=0.521$), height ($r=0.292$), and BMI ($r=0.468$), respectively.

We did not find such an association in the current study. It may be due to the differences in the age of selected patients or the protocol of management. However, the proportion of patients with a low level of FENa was lower in our study than in the mentioned study. This study had some limitations, including cross-sectional design, lack of control group consisting of a healthy population, lack of dietary evaluation, and small sample size. In addition, our findings would be more useful if we evaluate the association based on the genetic background of the patients, i.e., the different mutations of the CFTR gene and the pulmonary function of the patients.

Conclusion

Our findings indicated that most patients with a low level of FENa had normal serum sodium lev-

els. We did not find a significant association between FENa and growth parameters. The association had a trend to be significant for BMI. It is suggested that it may be due to appropriate follow-up of the studied population. However, it is recommended to plan more studies by including healthy subjects to obtain more accurate results.

Before designing the study, we assumed that due to the high consumption of salt in the Iranian diet, Iranian CF patients need less salt supplementation. However, according to the findings of this study, until our upcoming studies with larger sample sizes are performed, Iranian CF patients should continue to consume extra salt supplementation according to current guidelines.

Disclosure of conflict of interest

None.

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