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Original Article

Low sodium status in cystic fibrosis—as assessed by calculating fractional Na^+ excretion—is associated with decreased growth parameters

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Abstract

Background: In CF infants, normonatremic Na^+ depletion (NNaD), identified by fractional Na^+ excretion (FE_{Na}) values <0.5%, was recently linked to impaired growth. Our paper investigates the relationship between FE_{Na} and growth in CF children >2 years.
Methods: FE_{Na} values were calculated in 35 CF and 24 control children, and tested for correlations with *z*-scores for weight, height and BMI.
Results: All CF children and controls had normal plasma Na^+ concentrations. A total of 25 of 35 (71.4%) CF patients had decreased FE_{Na} values <0.5% (group I). FE_{Na} results of 10 CF patients (group II) and 23/24 controls (group III) were normal. In Na^+-depleted CF children, compared to normal controls, mean *z*-scores for weight (−0.18 ± 0.87 vs +1.03 ± 0.57, $p < 0.001$), height (−0.06 ± 0.89 vs +0.53 ± 0.72, $p = 0.009$) and BMI (−0.22 ± 0.87 vs +1.00 ± 1.06, $p < 0.001$) were significantly reduced. Also, we found positive correlations between FE_{Na} values and *z*-scores for weight ($r = 0.521$), height ($r = 0.292$) and BMI ($r = 0.468$), respectively.
Conclusion: NNaD may contribute to poor growth in CF.

Keywords: Cystic fibrosis; Normonatremic sodium depletion; Fractional sodium excretion; Growth retardation

1. Background

CF patients may be at risk for enhanced sodium loss particularly during periods of increased sweating or diarrhea [1–3]. While in hot countries this may manifest as hyponatremia in up to 95% of CF patients [4], plasma sodium concentrations in areas with moderate climates most often remain normal despite an actual state of sodium depletion [5]. Thus, in our institution, we have found a rate of hyponatremia of only 2%–3%. "Normonatremic sodium depletion" (NNaD) may thus not be recognized if sodium concentrations are measured only in blood. NNaD often manifests with only nonspecific symptomatology including a decrease in general well-being, listlessness, chronic fatigue, low blood pressure and anorexia [6–8]. However, it has recently been reported that even moderate states of sodium depletion may be associated with increased risk of morbidity and mortality [9]. Also, initially moderate NNaD may rapidly deteriorate to severe hyponatremia with serious complications including edema, muscle cramps, cerebral seizures, coma and death [10,11].

As an additional sequel, chronic sodium losses, e.g. due to ileostomy or colonic resection have been reported to cause failure to thrive [12,13] while normalization of sodium status was shown to reestablish normal weight gain and linear growth [14].

It thus appears prudent to diagnose sodium depletion as early as possible, i.e. before patients become severely hyponatremic. This may be particularly true for subjects with a known risk for enhanced sodium loss such as patients with renal salt-losing

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disorders, chronic diarrhea, ileostomy and CF. In this situation, and in the light of the limited ability of plasma or urine sodium concentration measurements to accurately assess body sodium balance, calculation of the fractional excretion of sodium which indicates the percentage of filtered sodium excreted in urine may be a useful tool [15,16]. FENa values below 0.5% have been reported to be associated with low sodium status and have been shown to accurately identify states of low sodium balance [15,16]. Moreover, calculation of the FE_{Na} compensates for urine flow rate and thus may reflect sodium status more appropriately than measurement of urine sodium concentrations alone.

The aim of our study was therefore (1) to investigate the incidence of NNaD using the determination of the FE_{Na} in CF patients in comparison with healthy controls, and (2) to evaluate the potential effect of sodium status on growth parameters in CF.

2. Methods

This prospective cross-sectional study included CF patients who were recruited during routine outpatient control visits between November 2013 and February 2014 in the Cystic Fibrosis Center of the Department of Pediatrics III, Medical University of Innsbruck. The study was approved by the ethics committee of the Medical University of Innsbruck. Written informed consent was obtained from a caregiver for each patient. Inclusion criteria were two positive sweat tests (sweat chloride >60 mmol/L), a homozygous CFTR mutation and an age between 2 and 18 years. Patients were excluded from the study if they had one of the following diagnoses: any kind of infectious or inflammatory disease, renal insufficiency (GFR < 60 mL/min/1.73 m^2), Bartter's syndrome, Gitelman's syndrome, diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion (SIADH), diabetes mellitus, edema, cardiac and/or hepatic insufficiency including CF-related liver disease and treatment with diuretics. These exclusion criteria were also applied for controls who were healthy children examined one day prior to minor elective surgery with uneventful patient histories and normal preoperative routine laboratory values.

Patient data were documented in the clinical data information system of the University Hospital of Innsbruck and the Cystic Fibrosis Center data collection system. Measurements of height and weight were performed in accordance with the Anthropometric Standardization Reference Manual [17]. Weight for age, height for age and body mass index (BMI) percentiles for girls and boys as well as the pertaining *z*-scores were determined using the respective CDC/NCHS pediatrics calculators [18]. Concentrations of electrolytes and creatinine in plasma and spot urine were determined using standard laboratory methods. To define sodium balance, the fractional excretion of sodium, i.e. FE_{Na} = urinary Na × plasma creatinine × 100/[plasma Na × urinary creatinine] (with all parameters expressed in mmol/L) was calculated. The normal range for FE_{Na} was chosen to be 0.5%–1.5% according to published literature [15,19].

We compared data on plasma Na, urine Na, FE_{Na} and *z*-scores for weight, height and BMI of children from the following three cohorts: CF-children with FE_{Na} values <0.5% (group I), CF-children with FE_{Na} > 0.5% (group II) and normal control children (group III). The Kolmogorov–Smirnov method was used to investigate if normal distribution of data for all sets of investigated parameters was given in the respective groups. Results were expressed as mean ± 1 SD. The Mann–Whitney *U* test was used to test for differences between the patient groups. A Spearman correlation rank test was performed for each individual patient group to explore the strength of relationship between FE_{Na} values and the *z*-weight, *z*-height and *z*-BMI variables. Spearman's *rho* was used to avoid that outliers as shown in the scatter plots of FE_{Na} versus growth variables exerted an influence on correlation size. A *p*-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 22®.

3. Results

A total of 35 CF patients (17 females, 18 males; age range, 2.5–16.9 years; mean age, 10.1 ± 4.2 years) were examined. Of the 24 healthy control subjects, aged 2.4 to 15.1 years (mean age 8.4 ± 3.5 years, not significantly different from CF children), 12 were females and 12 males.

Laboratory and growth parameters as well as calculated FE_{Na} values are summarized in Table 1 (CF children, groups I and II) and Table 2 (healthy controls, group III). Plasma sodium concentrations were between 135 and 144 mmol/L and thus normal in all CF patients and controls. Sodium concentrations in urine (uNa) were very variable in all three groups (Tables 1 and 2) and were between 10 and 235 mmol/L in group I, 110 and 250 mmol/L in group II and 25 and 245 mmol/L in controls (group III) with a mean uNa being significantly lower in group I (94.0 ± 50.5 mmol/L) as compared to group II (171.1 ± 39.2 mmol/L, $p < 0.01$) and group III (167.4 ± 63.3 mmol/L, $p < 0.01$) (Table 3).

FE_{Na} percentages were below normal (<0.5%) in 25/35 CF patients (group I, Table 1). The mean FE_{Na} value for group I was 0.29% ± 0.11%, which was significantly lower than in the 10 CF patients with normal FE_{Na} values (group II, mean FE_{Na} 0.88% ± 0.43%, $p < 0.01$) and in the 24 normal healthy controls (group III, mean FE_{Na} 1.02% ± 0.26%, $p < 0.01$; Table 3). These data suggest that a large proportion of nearly three quarters of the CF patients in our study had FE_{Na} values below the cutoff point of 0.5% that is thought to indicate low sodium status.

Having characterized the three patient groups with regard to their sodium status, we compared the mean *z*-scores for weight, height and BMI in both groups of CF patients (groups I and II) to those of healthy controls (group III). Table 4 shows significantly decreased mean *z*-scores for weight (−0.18 ± 0.87 vs 1.03 ± 0.57; $p < 0.01$), height (−0.06 ± 0.89 vs 0.53 ± 0.72; $p < 0.01$) and BMI (−0.22 ± 0.87 vs 1.00 ± 1.06; $p < 0.01$), respectively, in the sodium-depleted group of CF patients (group I) as compared to the healthy control group III. Also, the mean *z*-scores for weight (0.52 ± 0.69; $p < 0.05$) and BMI (−0.06 ± 0.83; $p < 0.01$) of the CF patient cohort with FE_{Na} values above 0.5% (group II) were significantly lower than those of the normal control group III, whereas the mean *z*-scores for height were very similar for these

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Table 1
Anthropometric and sodium status data of CF patients.

CF Patient	Age	Sex	Weight	z-Weight	Height	z-Height	BMI	z-BMI	pNa	uNa	FE_{Na}
(#)	(yrs)	(f/m)	(kg)		(cm)		kg/m^2		(mmol/L)	(mmol/L)	(%)
Group I											FE_{Na} < 0.5%
1	14.9	m	53.4	−0.2	169.2	−0.1	18.7	−0.4	141	95	0.26
2	7.1	f	18.1	−1.8	114.6	−1.4	13.8	−1.3	137	66	0.26
3	8.9	f	27.4	−0.3	135.1	0.5	15.1	−0.7	139	55	0.35
4	6.7	m	21.1	−0.4	119.6	−0.1	14.8	−0.6	140	74	0.16
5	7.8	m	34.1	1.5	137.1	1.8	18.1	1.2	139	118	0.31
6	7.1	m	27.2	0.9	126.7	0.8	16.9	0.8	138	76	0.48
7	16.9	m	67.9	0.3	179.9	0.7	20.1	−0.1	138	106	0.41
8	14.7	f	53.1	0.2	157.8	−0.6	21.3	0.5	140	130	0.33
9	14.7	f	49.9	−0.2	158.2	−0.5	19.9	0.1	141	52	0.23
10	4.9	f	18.8	0.4	108.7	0.4	15.9	0.5	141	57	0.14
11	7.8	m	25.9	0.2	128.8	0.4	15.6	−0.1	139	162	0.41
12	9.1	m	27.6	−0.3	132.5	−0.3	15.7	−0.3	136	112	0.27
13	5.2	m	20.5	0.6	108.7	−0.3	17.3	1.3	138	144	0.39
14	10.2	m	34.1	0.2	134.5	−0.8	18.8	0.8	140	10	0.12
15	8.7	f	24.4	−0.9	128.2	−0.5	14.8	−0.7	137	120	0.47
16	6.6	m	23.9	0.5	119.1	−0.1	16.8	0.9	137	104	0.29
17	14.7	f	44.7	−0.9	155.9	−0.9	18.4	−0.5	140	235	0.38
18	16.4	f	52.9	−0.2	165.2	0.4	19.4	−0.4	138	75	0.31
19	2.7	m	11.2	−2.1	89.1	−1.1	14.1	−2.1	139	140	0.27
20	4.4	f	18.9	0.8	115.5	2.6	14.2	−1.1	141	149	0.29
21	2.5	f	14.2	0.7	88.5	−0.6	15.6	−0.3	138	73	0.22
22	11.1	f	36.2	−0.3	145.4	−0.1	17.1	−0.2	138	102	0.31
23	16.2	f	43.9	−1.6	163.5	−0.1	16.4	−1.9	138	45	0.39
24	8.1	f	22.4	−1.1	124.1	−0.7	14.5	−0.8	138	24	0.16
25	12.1	m	36.6	−0.6	143.7	−0.9	17.7	−0.1	135	26	0.06
Group II											FE_{Na} > 0.5%
1	12.4	f	38.7	−0.5	153.5	−0.1	16.4	−0.8	142	137	1.97
2	11.7	m	41.3	0.3	151.5	0.6	18.1	0.2	139	250	1.14
3	10.2	m	32.9	0.1	145.8	0.9	15.5	−0.7	140	148	0.81
4	5.8	f	23.2	1.1	123.4	1.9	15.2	−0.1	140	110	0.77
5	6.9	f	26.9	1.1	131.5	1.9	15.6	0.1	139	171	0.71
6	8.9	m	28.5	0.1	135.3	0.4	15.5	−0.7	137	180	0.66
7	16.9	m	61.3	−0.2	167.5	0.1	21.8	0.2	140	190	1.04
8	12.1	m	44.7	0.4	161.8	1.6	17.1	−0.4	140	197	0.66
9	13.5	m	61.4	1.1	163.1	0.3	23.1	1.2	139	186	0.53
10	14.6	f	73.9	1.7	161.8	0.1	28.2	1.7	140	142	0.51

two groups (Table 4). This raises the question as to whether sodium depletion may have more effect on gain of weight as opposed to longitudinal growth.

To further evaluate possible associations between sodium status and physical development, we calculated correlations between FE_{Na} values and the respective z-scores for weight ($y = 0.34 + 1.2x$; $r = 0.521$; $p < 0.01$; Fig. 1), height ($y = 0.09 + 0.59x$; $r = 0.292$; $p < 0.05$ Fig. 2), and BMI ($y = 0.51 + 1.21x$; $r = 0.468$; $p < 0.01$; Fig. 1a–c), which were significant for all three parameters. Again, the smaller level of significance for the correlation between FE_{Na} and longitudinal growth suggested that sodium depletion as diagnosed by low FE_{Na} values may affect weight gain more than longitudinal growth.

4. Discussion

Our study supports the hypothesis that many CF patients may suffer from sodium deprivation even if their plasma sodium concentrations are normal [15]. We found that a majority of normonatremic CF patients (71.4%) had calculated FE_{Na} values of less than 0.5%, which is the previously reported lower limit of normal sodium status [15,16,19]. Accordingly, the mean FE_{Na} value of CF group I was significantly lower than that of group II with patients having normal FE_{Na} values above 0.5%, and that of normal controls (Table 3).These findings illustrate that in addition to CF patients with hyponatremia [1–4], a much larger proportion of CF subjects than hitherto recognized may be sodium-depleted. The determination of the FE_{Na} should therefore reveal previously undiagnosed NNaD [15], which might in part be responsible for a variety of subtle but well-known symptoms such as decreased general well-being, low blood pressure or failure to thrive. Coates et al. [15] were the first to address this problem in CF infants and proposed to supplement these patients with higher doses of sodium than recommended by a UK consensus report [5]. Our findings in older CF children are in full agreement with those of Coates et al. and suggest that CF patients should be regularly monitored for their sodium status and, if necessary, provided with higher sodium supplements.

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Table 2
Anthropometric and sodium status data of normal controls.

Control	Age	Sex	Weight	z-Weight	Height	z-Height	BMI	z-BMI	pNa	uNa	FE_{Na}
(#)	(years)	(f/m)	(kg)		(cm)		(kg/m^2)		(mmol/L)	(mmol/L)	(%)
Group III											
1	6.1	m	20.2	−0.2	123.5	1.4	13.1	−2.3	136	173	0.73
2	5.2	m	22.1	1.1	115.4	1.1	16.6	0.9	139	205	0.96
3	13.9	f	62.2	1.1	161.2	0.2	23.9	1.2	141	246	0.97
4	7.1	m	28.9	1.3	123.9	0.2	18.8	1.5	137	193	1.27
5	4.6	f	25.1	1.1	109.7	1.1	20.9	2.4	141	179	1.49
6	5.6	m	24.4	1.4	116.7	0.8	17.9	1.5	139	101	0.82
7	3.1	m	18.3	1.9	109.1	3.1	15.4	−0.5	139	127	1.02
8	9.6	f	40.1	1.2	141.4	0.8	20.1	1.1	140	88	1.16
9	8.1	f	32.5	1.2	132.3	0.7	18.6	1.1	140	99	1.14
10	7.4	m	23.1	−0.2	125.1	0.2	14.8	−0.6	141	25	0.47
11	5.9	m	24.2	1.2	116.3	0.3	17.9	1.5	139	205	0.96
12	12.8	m	53.3	0.9	152.8	−0.2	22.8	1.3	140	250	0.93
13	10.1	f	39.2	0.8	144.2	0.8	18.9	0.7	136	98	0.83
14	2.4	f	13.2	0.4	87.2	−0.4	17.4	0.9	142	79	0.53
15	10.5	f	49.2	1.5	142.5	0.2	24.2	1.7	137	135	1.02
16	7.1	f	30.1	1.4	125.4	0.5	19.1	1.5	137	202	1.32
17	15.1	m	68.9	1.1	169.9	−0.1	23.9	1.1	139	177	0.99
18	8.6	f	39.5	1.7	129.7	−0.2	23.5	2.1	144	241	1.34
19	4.7	m	23.1	1.9	106.6	−0.1	20.3	2.7	140	205	1.28
20	9.3	f	35.7	0.9	134.1	0.1	19.9	1.2	138	106	0.96
21	9.7	m	41.2	1.4	140.1	0.5	20.9	1.5	137	199	1.26
22	9.9	f	41.7	1.2	141.8	0.7	20.7	1.3	140	224	1.33
23	14.1	f	49.8	0.1	166.2	0.8	18.1	−0.5	141	246	0.97
24	11.4	f	41.9	0.4	146.6	0.1	19.5	0.6	140	214	0.75

The second important finding of our study was that NNaD, although thought to be a less pronounced state of sodium depletion, may be associated with failure to thrive in children with CF. It has long been known but scarcely appreciated in clinical practice that hyponatremia per se may cause impairment of weight gain as well as longitudinal growth [12–14,20–24]. Wassner [20,21] has shown that growth failure in sodium-depleted rats (1) affects both length and weight gain, and (2) is not necessarily associated with decreased nutrient and calorie intake. In a child with colonic resection, Wassner furthermore showed that chronic salt depletion was the sole cause of diminished linear growth [14], which could be restored to normal following appropriate sodium repletion. Also, there are numerous studies describing sodium depletion caused by chronic renal [24] or gastrointestinal sodium losses [12,14,25,26] as well as by dietary sodium restriction as a possible factor responsible for failure to thrive.

Table 3
Sodium concentrations in plasma (pNa) and urine (uNa), and mean FE_{Na} of CF patients with FE_{Na} < 0.5%, CF patients with FE_{Na} > 0.5%, and normal controls. 1, 2, 3

Patient group	CF FE_{Na} < 0.5%	CF FE_{Na} > 0.5%	Normal controls
pNa (mmol/L) [1)]	138.6 ± 1.6	139.6 ± 1.3	139.3 ± 2.0
uNa (mmol/L) [2)]	94.0 ± 50.5	171.1 ± 39.2	167.4 ± 63.3
FE_{Na} (%) [3)]	0.29 ± 0.11	0.88 ± 0.43	1.02 ± 0.26

Values given are mean ± 1 standard deviation. Differences for each parameter were calculated using the Mann–Whitney *U* test.

[1)] Plasma sodium concentration: no significant differences between the three groups.

[2)] Urine sodium concentration: mean uNa of the CF FE_{Na} < 0.5% cohort (group I) significantly lower than in the CF FE_{Na} > 0.5% cohort (group II, $p < 0.01$) and in normal controls (group III, $p < 0.01$).

[3)] Fractional excretion of sodium: mean FE_{Na} value of the CF FE_{Na} < 0.5% cohort (group I) significantly lower than in the CF FE_{Na} > 0.5% cohort (group II, $p < 0.01$) and in normal controls (group III, $p < 0.01$).

Table 4
Comparison of anthropometric data of CF patients with FENa <0.5% (group I), CF patients with FENa >0.5% (group II), and normal controls (group III). 1), 2), 3), 4), 5), 6)

Patient group	I (CF FENa < 0.5%)	II (CF FENa > 0.5%)	III (Normal controls FENa)
z-weight	−0.18 ± 0.87 [1)]	+0.52 ± 0.69 [2)]	+1.03 ± 0.57
z-height	−0.06 ± 0.89 [3)]	+0.77 ± 0.77 [4)]	+0.53 ± 0.72
z-BMI	−0.22 ± 0.87 [5)]	−0.06 ± 0.83 [6)]	+1.00 ± 1.06

z = *z*-score (standard score, the number of standard deviations a value is above the mean). Values given are mean ± 1 standard deviation. *p*-values calculated by Mann–Whitney *U* test.

[1)] *z*-weight of CF FENa < 0.5% cohort (group I) significantly lower than in the CF FENa > 0.5% cohort (Group II, $p < 0.05$) and in the normal controls cohort (group III, $p < 0.01$).

[2)] *z*-weight of CF FENa > 0.5% cohort (group I) significantly lower than in the normal controls cohort (group III, $p < 0.05$).

[3)] *z*-height of CF FENa < 0.5% cohort (group I) significantly lower than in the CF FENa >0.5% cohort (group II, $p < 0.05$) and in the normal controls cohort (group III, $p < 0.01$).

[4)] *z*-height of CF FENa > 0.5% cohort (group II) not significantly different from normal control (group III, $p = 0.985$).

[5)] *z*-BMI of CF FENa < 0.5% cohort (group I) not significantly lower than in the CF FENa > 0.5% cohort (group II, $p = 0.578$) but significantly lower than in normal controls cohort (group III, $p < 0.01$).

[6)] *z*-BMI of CF FENa > 0.5% cohort (group I) significantly lower than in the normal controls cohort (group III, $p < 0.01$).

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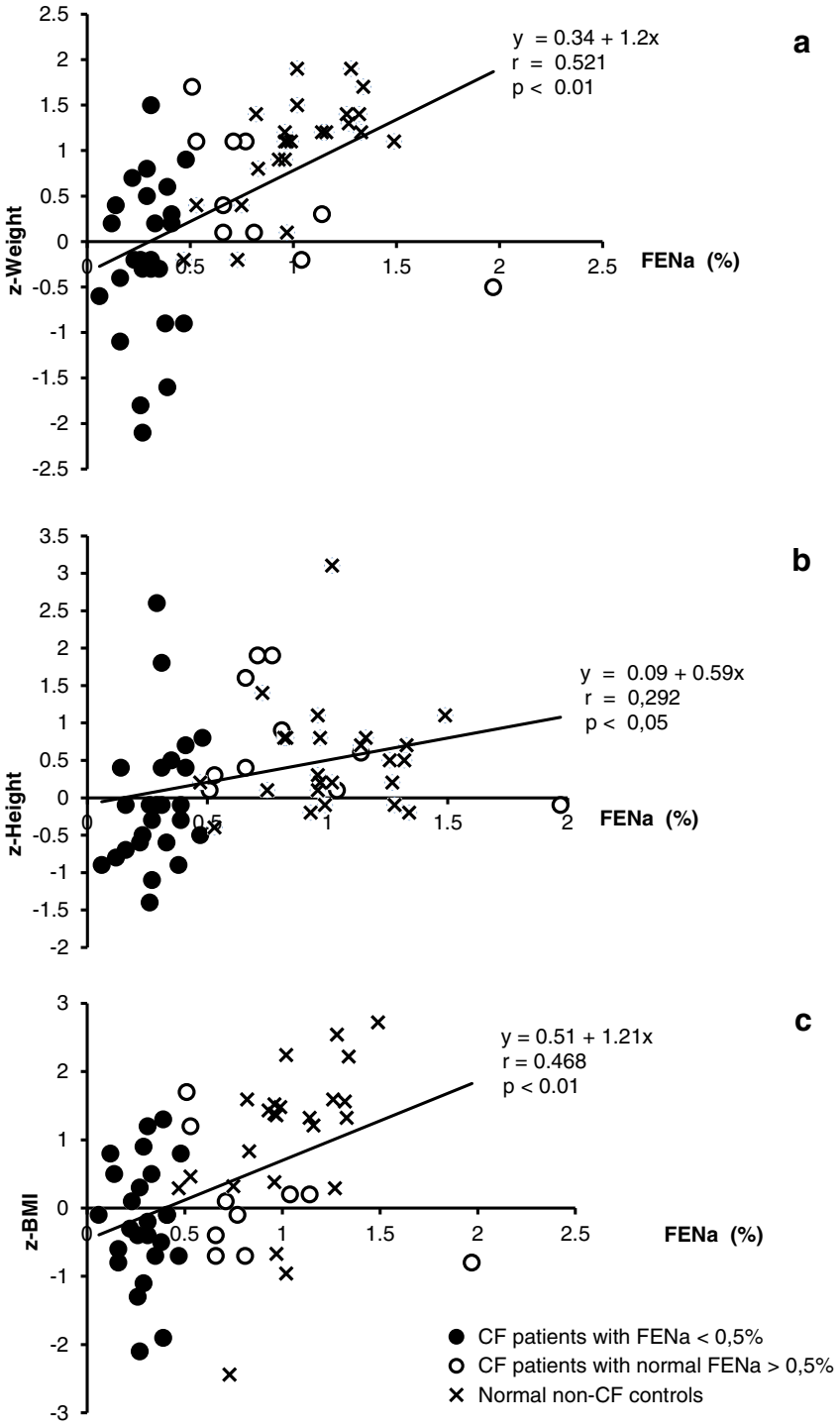

Fig. 1. Correlations between FE_{Na} values and *z*-scores for weight (1a), height (1b) and BMI (1c) of CF patients with low FE_{Na} (<0.5%,●), CF patients with normal FE_{Na} (>0.5%, ○) and nonCF normal controls (×).

In CF children beyond infant age, there are, to our knowledge, no published studies that have investigated the impact of NNaD on growth. We have therefore compared normonatremic CF patients with low FE_{Na} to normonatremic CF patients with normal FE_{Na} and to healthy non-CF controls with regard to their physical development in correlation with their sodium status. We found that the mean *z*-scores for weight, height and BMI were significantly decreased in the CF cohort with FE_{Na} values <0.5% as compared to normal controls (Table 4). Furthermore, the mean *z*-scores for weight and height of CF patients with FE_{Na} values <0.5% (group I) were also significantly lower than those of CF patients with normal FE_{Na} (group II) (Table 4). Taken together, these findings suggest that even rather moderate sodium depletion as seen in NNaD may negatively affect both weight gain and longitudinal growth and thus support a substantial role for sodium in the physical

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development of children. Also, the *z*-score for height of CF patients from group II with normal sodium balance did not significantly differ from that in healthy controls which further suggests that in CF children longitudinal growth may be hampered to a lesser degree as long as physiological sodium balance is maintained even if other CF-associated nutritional deficiencies are in effect. This may indicate that normal sodium balance may help reduce the retarding effects of other nutritional deficiencies on longitudinal growth despite already existing reduced weight gain. Our findings of decreased mean *z*-scores of weight, longitudinal growth and BMI in sodium-depleted CF patients are further substantiated by moderate but constant correlations with the respective FE_{Na} values in the three patient groups (Fig. 1a–c).

Thus, our study, in agreement with the report by Coates et al. [15], demonstrates that CF may be one of the many chronic diseases in which enhanced salt loss is a factor in failure to thrive. Moreover, it is shown that even moderate sodium depletion manifesting as NNaD may be an eminent cause of the difficulties in thriving so characteristic for many CF children. However, the distinct mechanism by which even such a minor disturbance of sodium balance may affect growth remains to be elucidated.

Our study has a variety of limitations: first of all, we have simply compared cross-sectional data on parameters of sodium status and growth whereas other measures influencing growth such as the amount of nutrients, calories and salt ingested, as well as the quality of the digestive function and the impact of increased energy consumption due to greater respiratory work of CF patients were not regarded. Second, due to the small number of patients in our study, no attempt was made to correlate sodium status with different types of *CFTR* mutations. Considering recent reports linking specific *CFTR* mutations to hyponatremia [27,28] this question deserves further evaluation. Third, while chloride has been implicated in failure to thrive due to hypochloremia in patients with congenital chloride diarrhea [29], we did not investigate whether and to what degree chloride might be involved in growth failure of our NNaD patients.

In summary, we have shown in a small cohort that a majority of CF patients, although being normonatremic, may suffer from hitherto unrecognized sodium depletion. We have also found that low FE_{Na} values were associated with decreased growth parameters in CF patients. We therefore believe that CF patients may benefit from regular testing of their sodium status using the calculation of FE_{Na} values in order to prevent growth failure and other complications following NNaD.

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