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Sara Elsayed Ali Abozaid
Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta, Egypt

Mai Rabie Elsheikh
Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta, Egypt

Maaly Mohamed Mabrouk
Department of Clinical Pathology, Faculty of Medicine, Tanta University, Tanta, Egypt

Maher Ahmed Abel Hafez
Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta, Egypt

Corresponding Author:
Sara Elsayed Ali Abozaid
Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta, Egypt

Urinary calcium creatinine ratio in breast fed and artificial fed healthy infants

Sara Elsayed Ali Abozaid, Mai Rabie Elsheikh, Maaly Mohamed Mabrouk and Maher Ahmed Abel Hafez

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Abstract
Background: The normative standard for infant feeding is exclusive breastfeeding for the initial six months of life, followed by continued breastfeeding for a duration of two years. The aim is to compare urinary Calcium/creatinine ratio between artificial fed and breast fed healthy infants.
Methods: This cross-sectional comparative study was carried out upon 80 healthy full-term infants at the out-patient clinic of Pediatric Department, Tanta University hospital during the period from December 2021 to December 2022. Inclusion criteria were infants with age ranging from 2-6 months, Healthy infants, Exclusive breast feeding, Exclusive artificial feeding. The infants were divided into two groups according to the type of feeding: Group A: 40 healthy born full term exclusively artificial fed infants. Group B: 40 healthy born full term exclusively breast-fed infants.
Results: A urinary calcium creatinine ratio that was significantly higher in artifical fed infants compared to breast fed infants was observed. And age exhibits a negative significant correlation with the Ca/Creat ratio, however in both groups, no correlation was found to be statistically significant between the Ca/Creat ratio and Hb, PLTs, TLC, urea, creat, CRP, Na, Ca T, Ca I, Mg, Ph, and anthropometric measurements.
Conclusions: A higher level of UCa/Cr is observed in infants who are artificially fed due to the higher sodium content in artificial milk, which influences calcium excretion during the first few months of life and This observation could potentially suggest that maintaining a low-sodium diet is crucial in order to prevent the impact of developing urinary tract stones and hypercalciuria.

Keywords: Urinary calcium creatinine ratio, breast fed, artificial fed healthy

Introduction

The normative standard for infant feeding is exclusive breastfeeding during the initial six months of life, followed by continued breastfeeding for two years [1, 2]. Breast milk possesses nonnutritive bioactive factors that promote survival and healthy development, in addition to its nutritional composition, which are both uniquely suited to the infant. As even the most advanced synthetic formulas are unable to completely substitute breast milk, transitioning to artificial feeding induces "metabolic stress" in infants [3, 4].

During the first few months of life, the benchmark for nutrient absorption and bioavailability is an infant who is exclusively fed human milk. Infant formulas contain a greater quantity of minerals, including calcium, than breast milk does due to the potential for reduced bioavailability. While infant formulas may contain varying concentrations of calcium, it is critical to ensure that the total calcium absorption from the formula is equivalent to or greater than the amount of calcium found in breast milk [5].

Calcium is actively transferred to the foetus during healthy pregnancies, resulting in substantial mineral accumulation during the final trimester. Subsequent to birth, the infant relies on dietary sources for mineral nutrition [6].

Urinary excretion serves as a reliable indicator of mineral status. The prevailing approach for assessing typical calcium excretion involves the 24-hour collection of urine [7]. Nevertheless, the process of 24-hour urine collection in children is laborious and insufficient [8], As opposed to relying on spot urinary Calcium/Creatinine ratio estimation, which is more convenient and practical.

Creatinine can be utilised to express the results of a random calcium measurement in the urine. A value below 0.14 is considered normal for the urinary calcium-to-creatinine ratio (UCa/Cr) in children. Patients who have hypercalciuria exhibit values that surpass 0.20.

Time causes a gradual decline in the UCa/Cr ratio in children. It is critical to acknowledge this fact as the majority of children will be erroneously identified as hypercalcitic when adult cut-offs are applied [9]. It is recommended that infants below the age of six months have UCa/Cr ratio levels of 0.80 mg/mg [10].

One of the most significant determinants impacting urinary calcium excretion is dietary intake. Intakes of dietary calcium, sodium, protein, potassium, and phosphorus have a substantial impact on urinary calcium excretion [11]. Furthermore, the concentrations of these substances in human milk differ from those in formulas. Calcium absorption is dependent on sodium absorption because 90% of the process takes place as a paracellular transmission in the proximal tubule and Thick ascending limb of Henle Increasing the dosage of sodium chloride, whether administered orally or intravenously, hinders the net absorption of calcium into the renal tubules. This inhibitory effect is beneficial in the treatment of hypercalcemia, as it increases urinary calcium excretion. This is because excessive calcium delivery to the distal nephron for transcellular absorption may overwhelm the distal nephron, resulting in obligatory hypercalciuria [11]. Protein consumption also elevates urinary calcium excretion in tandem with increased net acid excretion due to the liberation of protons produced when sulphur oxidation in amino acids takes place [11], therefore, it increases gradually in proportion to the protein intake. Additional variables that may influence calcium excretion include ethnicity, genetics, sun exposure, and dietary patterns [12].

We aimed to compare urinary Calcium/creatinine ratio between breasts fed and artificial fed healthy infants.

Patients and Methods

This cross-sectional comparative study was carried out upon 80 healthy full-term infants at the out-patient clinic of Pediatric Department, Tanta University hospital during the period from December 2021 to December 2022.This study was approved by the ethical committee of the faculty of medicine (No. 35217/1/22), and informed consent was obtained from the parents.

Inclusion criteria were infants with age ranging from 2-6 months, Healthy infants, Exclusive breast feeding, or Exclusive artificial feeding.

Exclusion criteria were start of weaning, Complementary or supplementary feeding, Maternal illness during pregnancy, Infants with chronic diseases or syndromic facies.

The infants were divided into two groups according to the type of feeding:

Group A

40 healthy full term exclusively artificial fed infants of age ranging from two to six months.

Group B

40 healthy full term exclusively breast-fed infants of age ranging from two to six months.

All patients were subjected

History taking with special emphasis on dietitic history.

Careful physical examination including

Vital signs, anthropometric measurements and systemic examination for chest. Heart, abdomen and neurological assessment.

Laboratory investigations

Blood samples were obtained from all cases and control groups for the following: Renal function tests (RFTs), serum electrolytes (sodium, magnesium, phosphorus, calcium total, ionized), complete blood picture (CBC) and CRP.

Urine samples: Spot morning Urine samples collected at using a collection bag in chemically clean bottles and were brought to the laboratory, where samples were analyzed within 3 to 4 hours after sampling for complete urine analysis, calcium /creatinine ratio in urine.

Research investigation

Urinary calcium /creatinine ratio urine by konelab PRIME 60i.

Samples collection

Peripheral venous blood sampling for the laboratory work up was performed after written consent. A blood sample was withdrawn by venepuncture after cleaning the skin by 70% alcohol.

1. **Renal function tests, CRP Serum electrolytes (Ca, Pm, Mg)**
   Supplied by automated INDIKO PLUS apparatus.

2. **Complete blood count (CBC)**
   Using ERMA INC. apparatus fully automatic blood cell counter.

3. **Plasma Na**
   Plasma Na was estimated by ST-200 Plus Electrolyte Analyser

4. **Urine analysis**
   Random spot urine analysis was conducted to assess urinary solute levels and identify the presence of urinary tract infections.

Radiological investigations including

Renal ultrasound on the infants was performed using a linear ultrasound (5–7.5 MHz) probe. For detection or exclusion any anomaly or pathology in renal system .The analysis excluded infants who exhibited renal anomalies as detected by the ultrasound.

Statistical analysis

SPSS v27 was utilised for the statistical analysis (IBM2, Armonk, NY, USA).Histograms and the Shapiro-Wilks test were utilised to assess the normality of the data distribution. The means and standard deviations (SD) of quantitative parametric data were utilised for analysis via the ANOVA (F) test. Analyses utilising the Chi-square test were conducted on qualitative variables expressed as frequency and percentage (%). A two-tailed P value less than 0.05 was deemed to indicate statistical significance. The degree of correlation between two quantitative variables was estimated using Pearson correlation.

Results

As regard age, sex and perinatal history, this table shows that artificial feeding and breastfeeding did not differ statistically significantly. (p =0.390, 0.366, 0.569 respectively). A comparison between artificial fed and breast-fed infants did not yield any statistically significant results as regard weight, length, and head circumference (p= 0.153, 0.195, 0.107 respectively). Table (1)

Table 1: Demographic data of the studied groups

		Group				T-Test	
		Artificial		Breast		t	P-value
Age (Months)	**Range**	2 - 6		2 - 6		-0.864	0.390
	Mean ±SD	5.025 ± 1.143		5.238 ± 1.056			
Chi-Square		**N**	**%**	**N**	**%**	**X^2**	**P-value**
Sex	Male	15(37.50%)		19(47.50%)		0.818	0.366
	Female	25(62.50%)		21(52.50%)			
Perinatal history	Negative	37(92.50%)		34(85.00%)		1.127	0.569
	Pre-eclampsia	2(5.00%)		4(10.00			
	Diabetic	1 (2.50%)		2 (5.00%)			
Weight (kg)	Range	5 - 7.5		5 - 7.6		-1.442	0.153
	Mean ±SD	6.273 ± 0.837		6.543 ± 0.884			
Length (cm)	Range	58 - 69		58 - 69		-1.309	0.195
	Mean ±SD	64.675 ± 3.526		65.625 ± 2.941			
Head circumference (cm)	Range	39 - 44		38 - 44		-1.631	0.107
	Mean ±SD	41.650 ± 1.167		42.075 ± 1.163			

X2: Chi square test, p: p value for comparing between the studied groups

No statistically significant difference was observed. between artificial fed and breast fed infants regarding Sodium, Total Calcium, Ionized Calcium, Magnesium and phosphorus serum levels in Artificial fed and Breast fed infants (p= 0.367, 0.545, 0.674, 0.744, 0.835repectively). There was statistically significant higher urinary calcium creatinine ratio in artificial fed infants as compared to breast fed infants (p= <0.001). The observed difference had no statistical significance. Between artificial fed and breast-fed infants as regard Hemoglobin, Platelets, Total Leukocytic Count, urea, creatinine, and CRP and urine analysis (p=0.363, 0.093, 0.828, 0.130, 0.167, 0.703, 0.305 respectively). Table (2)

Table 2: Comparison between the studied groups as regard serum electrolytes (Na, total Ca, ionized Ca, Mg, P) and Urinary Ca/Creat ratio

		Group		T-Test	
		Artificial	**Breast**	**T**	**P-value**
Serum Na (mmol/l)	Range	137 - 143.3	134 - 144	-0.908	0.367
	Mean ±SD	138.895 ± 1.955	138.480 ± 2.129		
Serum Ca T (mg/dl)	Range	9 - 11.5	8.4 - 11	0.608	0.545
	Mean ±SD	10.445 ± 0.672	10.350 ± 0.724		
Serum Ca I (mmol/l)	Range	1.1 - 1.4	1 - 1.3	0.422	0.674
	Mean ±SD	1.218 ± 0.063	1.215 ± 0.071		
Serum Mg (mg/dl)	Range	1.7 - 2.6	1.64 - 2.3	0.328	0.744
	Mean ±SD	1.968 ± 0.180	1.955 ± 0.174		
Serum P (mg/dl)	Range	4.9 - 7.5	4 - 7	-0.209	0.835
	Mean ±SD	5.860 ± 0.548	5.890 ± 0.726		
Urinary Ca/Creat ratio	Range	0.21 - 0.9	0.05 - 0.65	8.499	<0.001*
	Mean ±SD	0.531 ± 0.170	0.235 ± 0.139		
Hb (g/dl)	Range	10.5 - 11.8	10 - 11.7	0.915	0.363
	Mean ±SD	11.015 ± 0.366	10.915 ± 0.586		
PLTs (/ul)	Range	197 - 450	227 - 400	1.700	0.093
	Mean ±SD	370.725 ± 70.108	347.600 ± 49.850		
TLC (/ul)	Range	5.5 - 13.5	5 - 14.6	-0.218	0.828
	Mean ±SD	6.985 ± 1.923	7.077±1.831		
Urea (mg/dl)	Range	10 - 18	11 - 19	-1.531	0.130
	Mean ±SD	13.275 ± 2.063	14.000 ± 2.172		
Creat (mg/dl)	Range	0.35 - 0.8	0.34 - 0.61	1.394	0.167
	Mean ±SD	0.495 ± 0.110	0.465 ± 0.080		
CRP (mg/l)	Range	5 - 6	5 - 7	-0.382	0.703
	Mean ±SD	5.050 ± 0.221	5.075 ± 0.350		
Urine analysis	Normal	37(92.50%)	39(97.50%)	1.053	0.305
	Abnormal	3(7.50%)	1(2.50%)		

t: Student t-test
p: p value for comparing between the studied groups
Na=sodium, Ca T= total calcium, Ca I =ionized calcium, Mg= magnesium, P= Phosphorus, Hb= hemoglobin, PLTs= platelets, TLC= total Leukocytic Count, creat= creatinine, CRP=c reactive protein.

In both groups, the Ca/Creat ratio was not statistically significantly correlated with anthropometric measurements; however, age and Ca/Creat ratio exhibited a statistically significant negative correlation. Table (3)

Table 3: Correlation between Urinary Ca/Creat ratio and different parameters in the studied groups

Correlations		
	UCa/Creat ratio	
	r	P-value
Age (Months)	-0.248	0.026*
Weight (kg)	-0.140	0.214
Length (cm)	-0.197	0.079
Head circumference (cm)	-0.194	0.085

r: Pearson coefficient
*: Statistically significant at $p \leq 0.05$

There was no statistically significant between Ca/Creat ratio and Hb, PLTs, TLC, urea, creat, CRP, Na, Ca T, Ca I, Mg, Ph. Table (4)

Table 4: Correlation between Urinary Ca/Creat ratio and different parameters in the studied groups

Correlations		
	Ca/Creat ratio	
	r	P-value
Hb (g/dl)	0.198	0.078
PLTs (/ul)	0.023	0.842
TLC (/ul)	0.080	0.482
Urea (mg/dl)	-0.132	0.244
Creat (mg/dl)	0.077	0.500
CRP (mg/l)	-0.005	0.965
Serum Na (mmol/l)	0.008	0.943
Serum Ca T (mg/dl)	-0.007	0.953
Serum Ca I (mmol/l)	0.104	0.361
Serum Mg (mg/dl)	0.115	0.311
Serum P (mg/dl)	-0.026	0.820

r: Pearson coefficient
*: Statistically significant at $p \leq 0.05$
Hb= hemoglobin, PLTs= platelets, TLC= total Leukocytic Count, creat= creatinine, CRP= c reactive protein, Na=sodium, Ca T= total calcium, Ca I =ionized calcium, Mg= magnesium, P=phosphorus.

Discussion

In this study we found that UCa/Cr was statistically significant higher in artificial fed than breast fed healthy infants. This could be explained by:

1. Higher protein content in artificial milk when compared with protein content in breast milk which leads to a corresponding rise in net acid excretion due to release of protons from oxidation of sulfur in the amino acids, This acidification subsequently stimulates the action of buffer systems including calcium phosphate in bones, which results in increase in calcium excretion [13] or via a reduction in renal tubular calcium reabsorption [14]. Additionally, protein intake may enhance urinary calcium excretion through increased intestinal calcium absorption [15].
2. Higher sodium content in artificial milk when compared with sodium content in breast milk. As calcium absorption occurs in the proximal tubule and TALH at the mercy of sodium absorption due to competition between sodium and calcium ions in the renal tubule [16].

This agree with the prospective randomized clinical trial performed by Ferré *et al.*, [17] which showed that the high protein formulation significantly increased the urinary Ca/Cr ratio, according to this study [17].

Consistent with our research, Cillo *et al.*, [18] who performed a study on 104 healthy newborns had found that neonates that were exclusively fed artificial milk exhibited a significantly higher urinary excretion of Ca (mean 0.10±0.06) compared to those that were exclusively fed breast milk [18].

Our results comes in harmony with the study obtained by Erol *et al.* [19] Using 425 healthy children aged 0-5 years, this study aimed to establish age-specific reference values for UCa/Cr in healthy Turkish children and examine the effect of nutrition on UCa excretion in infants younger than six months. The findings of this research indicated that the mean of UCa/Cr ratio values in the breast-fed group were lower than those in the formula fed group [19].

This disagreed with the study performed by Ceran *et al.* [20] that showed that there was no significant differences between those breast-fed and those fed by mixed food (commercial formula, fruit juice and rice flour) in terms of the mean UCa/Cr [20].

Our explanation of this discrepancy may be due to different ages enrolled in their study, and weaning wasn't from inclusion criteria.

A notable negative correlation was observed between age and UCa/Cr in the present study. This may also be the result of immature tubules or impaired creatinine excretion. Due to the fact that creatinine is produced from creatine in muscle, its urinary excretion is subject to variation with the subject's muscle mass. [20] Infants have a higher UCa/Cr than older children and adults, and it decreases steadily with age until it reaches 0.21 mg/mg, the most commonly used threshold in adults that is also applicable in childhood.[21]

This agrees with the study performed by Ceran *et al.* [19] that showed a strong inverse relationship with age [19].

Whereas others have shown weak correlation as in the cross-sectional study performed in Aydın, in western Turkey by Sönmez *et al.* [22].

There is no correlation between UCa/Cr and weight in the present study.

This agree with the study obtained by Gül *et al.* [26] to determine the prevalence of hypercalciuria and percentiles of urinary calcium excretion among school-aged children in Tokat [23].

However, the study obtained by Cillo *et al.* [18] showed higher Ca excretion in newborns with a body weight less than 3 kg than those with body weight more than 3 Kg [18].

Limitations

The usage of a spot urine sample in the absence of feasible means to acquire a 24-hour urine sample from a large group of healthy infants. The levels of vitamin D and PTH were not evaluated.

Conclusion

Calcium excretion is influenced by the type of nutrition provided in the first few months of life. Infants who are artificially fed exhibit elevated levels of UCa/Cr possibly due to the higher sodium content in artificial milk. This finding may suggest that maintaining a low-sodium diet is crucial in order to prevent the development of hypercalciuria and urinary tract stones. Our findings revealed an inverse relationship between UCa/Cr and age; therefore, normal values for older children and adults should not be used in infant screening or monitoring. Young children and infants should have higher normal values recognised by clinicians.

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