Influence of Phototherapy on Urinary Calcium Excretion among Full Term Neonates

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ABSTRACT

Background: After 48 hours of phototherapy, the mean urinary Ca excretion is elevated in numerous neonates in previous studies.
Objective: This study aimed to evaluate phototherapy effects on urinary calcium excretion among full term neonates.
Patients and methods: This Prospective-cohort study was conducted on 30 term neonates presented in NICU of Pediatrics Department, Zagazig University Hospitals through the period from January 2018 to January 2019. They were exposed to phototherapy. We assessed urinary calcium and sodium excretion post-phototherapy in term neonates.
Results: As regards urinary calcium, our results revealed an increment in urinary calcium excretion of about 8.76% post-phototherapy exposure, which was significantly increased after phototherapy. A statistically significant increment in serum sodium after exposure to phototherapy was found. Considering urinary calcium, there was statistically significant increase in urine calcium after phototherapy in female patients aged ≥ 8 days born at gestational age less than 39 week and in those delivered by cesarean section. On the other hand, there was statistically significant decrease in calcium/creatinine ratio after phototherapy in patients delivered by cesarean section only
Conclusion: Despite presence of an increment in urinary calcium excretion after phototherapy, no significant difference was found in calcium/creatinine ratio after phototherapy, so no hypercalciuria to be considered, so it cannot cause hypocalcemia.
Keywords: Phototherapy, Urinary calcium excretion.

INTRODUCTION

Jaundice is the clinical manifestation of chemical hyperbilirubinemia. Jaundice appears on newborns when serum bilirubin concentration exceeds 5.0 mg/dl. Although clinically among adults, jaundice manifests as a yellowing of the skin and sclera due to accumulation of unconjugated bilirubin, and it only develops in adults if the blood bilirubin level is above 2.0 mg/dl **(1)**.

During the first week after delivery, hyperbilirubinemia affects 60% of term neonates and 80% of preterm neonates. Pigments of lipid-soluble, nonpolar, unconjugated bilirubin that have accumulated in the skin are typically to occur **(2)**. The condition known as icterus neonatorum, or newborn jaundice, has been recognised since the nineteenth century. When infants died of severe jaundice, doctors began using the term "kernicterus" to describe the characteristic yellow staining of the basal ganglia **(3)**.

Unconjugated hyperbilirubinemia is most often treated and prevented by phototherapy. Total bilirubin concentrations can be lowered by phototherapy in most infants despite differences in age, skin pigmentation, and hemolysis. Researchers have decided that phototherapy is a safe therapeutic option that can lessen infants' need for exchange transfusion after reviewing the results of prior research on the effect of the therapy and finding no major problems **(2)**. In rare cases, phototherapy problems can arise. Long-term exposure to phototherapy may cause retinal degeneration. The use of light in medical treatments can raise internal and external temperatures. As a result, phototherapy may cause dehydration, most notably by imperceptible water loss. Furthermore, bronze infant syndrome has been linked to phototherapy. Several hours after being placed in the phototherapy equipment, neonates with this syndrome will have a bronze coloration in their serum, urine, and skin. Inadequate safety measures can lead to additional problems like electric shock and burns **(4)**.

Hypocalcemia is a side effect of some phototherapy treatments. It is possible that phototherapy lowers melatonin levels, which in turn decreases glucocorticoid release and increases calcium (Ca) resorption, resulting in hypocalcemia **(5)**. After 48 hours of phototherapy, the average amount of Ca excreted in the urine of some newborns rose. First-week urinary Ca excretion is proportional to urinary Na excretion and gestational age. Urinary excretion of cyclic 3',5'-adenosine monophosphate and potassium can also be influenced by glomerular filtration, which can in turn alter Ca secretion **(6)**.

In Hooman and Honarpisheh (7) study, the risk of hypocalcemia from phototherapy was assessed. Seizures brought on by hypocalcemia could further harm the central nervous system (CNS) and exacerbate any damage caused by jaundice to the CNS. **Asl *et al.* (8)** measured the amount of calcium in the urine of full-term infants after phototherapy. The researchers concluded that, despite not causing hypocalcemia, phototherapy may promote calcium excretion through urination.

This study's purpose was to evaluate phototherapy effects on urinary calcium excretion among full term neonates.

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PATIENTS AND METHODS

Prospective-cohort study that was carried out on 30 term neonates, presented in NICU of Pediatric Department, Zagazig University Hospitals from January 2018 to January 2019. 18 of them (60%) were males and 12 of them (40%) were female, their ages ranged from 2 to 12 days with means of 5.9 ± 2.77 days, where 15 (50%) neonates aged 2-5 days, 7 (23.3%) neonates aged 6-7 days, and 8 (26.7%) neonates aged ≥ 8 days. 10 (33.3%) neonates were born by normal vaginal delivery (NVD) whereas 20 (66.7%) neonates were born by cesarean section (CS).

Inclusion Criteria:

More than 37 weeks at conception, or full term, weight at birth equal to or more than 2500 grams, age greater than two days, not having a record of icterus in the first two days of life, serum bilirubin concentration of 15-19 mg/dL indicating a need for phototherapy.

Exclusion Criteria:

Infants with hemolysis (jaundice after birth or within 24 hours), neonates needing exchange transfusion, asphyxia, infants of diabetic mothers, and mothers with history of hyperthyroidism, respiratory distress, infants with a history of intravenous fluid, sepsis, and neonates on antibiotic therapy.

Figure (1): from the 2004 American Academy of Pediatrics (AAP) Clinical Practice Guidelines illustrating the age and severity of TSB as criteria for intervention and the initiation of phototherapy [9]. Overhead phototherapy with four bulbs of the same wavelength, positioned 20 centimeters apart. The average phototherapy session lasted 24 hours, with some cases requiring up to 48 hours of treatment.

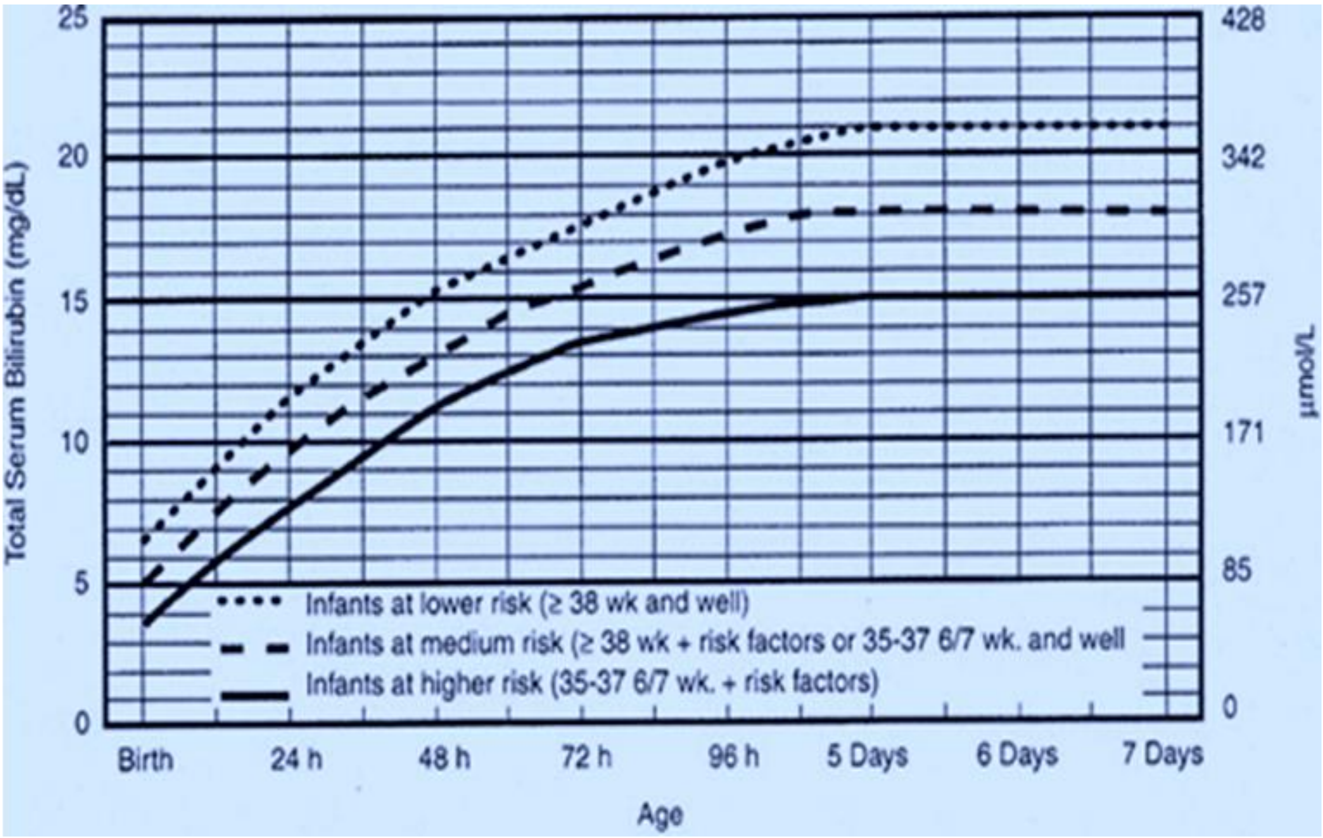

Figure (1): Procedures for administering phototherapy to neonates born at 35 weeks or later [9].

All studied groups underwent the following:

1) **History taking:** Full history was collected and family history of other sibling admitted to NICU, as well as family history.
2) **Clinical examination:** General examinations, vital signs, Jaundice assessment: The was neonate examined in good daylight. By paling the skin by digital pressure and the underlying color of skin and subcutaneous tissue should be noted.
3) **Routine investigation in the form of:** Hemoglobin level, blood grouping for mother and babies, reticulocyte count, and hematocrit value.
4) **Special investigation performed before and after phototherapy in the form of:** Total and direct bilirubin levels by colorimetric assay kit (K553-100**).** Serum and urinary creatinine levels using commercial kit provided by SPINREACT**.** Serum and urinary calcium levels using commercial kit provided by SPINREACT. Serum and urinary sodium levels using commercial kit provided by Atlas Medical and Biovision respectively. Urinary Ca/creatinine ratio (mg/mg) was calculated as random urinary calcium (mg/dL) excretion divided by random urinary creatinine excretion (mg/dL) **[10].** Fractional excretion of sodium (FeNa): FeNa = (Urine Na / Serum Na) / (Urine Cr / Serum Cr) *100 **[11].**

Collection of blood samples:

5 ml of venous blood sample was taken from every participant under complete aseptic condition and collected in sterile plane tubes and used measurement of hemoglobin level, reticulocyte count, total & direct bilirubin levels, serum creatinine, serum sodium and serum calcium.

Urine sampling:

Urine samples were collected from neonates prior to phototherapy by allowing them to urinate in a urinary bag for two hours after admission. The urine was then centrifuged at 15000 RPM for five minutes, and the supernatant was collected in Eppendorf tubes for analysis of urinary creatinine, sodium, and calcium levels.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. All parents of participants provided informed consents for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

In order to analyze the data acquired, Statistical Package of Social Sciences version 20 was used to execute it on a computer (SPSS). In order to convey the findings, tables and graphs were employed. The quantitative data were presented in the form of the mean, median, standard deviation, and confidence intervals. The information was presented using qualitative statistics such as frequency and percentage. The student's t test (T) is used to assess the data while dealing with quantitative independent variables. Pearson Chi-Square and Chi-Square for Linear Trend (X^2) were used to assess qualitatively independent data. The significance of a P value of 0.05 or less was determined.

RESULTS

Male gender represented 60% of the studied patients. Half of the studied group aged from 2 to 5 days with median age 5.5 days (Table 1).

Table (1): Distribution of the studied patients according to demographic characteristics

	N=30		%
Gender: Male Female	 18 12		 60 40
Age group: 2-5 days 6-7 days ≥ 8 days	 15 7 8		 50 23.3 26.7
	Mean ± SD	**Median**	**Range (min-max)**
Age(days)	5.9 ± 2.77	5.5	2 – 12

There was statistically significant difference between total bilirubin as well as indirect bilirubin before and after phototherapy (Table 2).

Table (2): Comparison between levels of serum bilirubin among the studied patients before and after phototherapy

	Before	After	t	p	Sig
	Mean ± SD	**Mean ± SD**			
Total bilirubin (mg/dl)	16.67 ± 1.41	12.23 ± 1.36	27.603	<0.001	HS
	Mean ± SD	**Mean ± SD**	Z	P	
Indirect bilirubin (mg/dl)	16.44 ± 1.43	11.89 ± 1.38	27.72	<0.001	HS

There was statistically significant increase in urine calcium after phototherapy in female patients, in patients aged ≥ 8 days, born at gestational age less than 39 week and in those delivered by cesarean section. On the other hand, there was statistically non-significant change in urine calcium after phototherapy in relation to body weight and level of total bilirubin (Table 3).

Table (3): Comparison between urine calcium levels before and after therapy in relation to demographic and clinical data of the studied patients

	Urinary calcium				
	Before	After	T	P	Sig
	Mean ± SD	Mean ± SD			
Gender:					
Male	8.91 ± 1.56	9.34 ± 1.68	-1.167	0.259	NS
Female	8.86 ± 1.85	10.13 ± 2.36	-3.377	0.006	S
Age:					
2-5 days	9.07 ± 1.96	9.59 ± 2.22	-1.229	0.239	NS
6-7 days	9.06 ± 1.2	9.56 ± 1.74	-0.933	0.387	NS
≥ 8 days	8.4±1.14	9.86±1.93	-3.424	0.011	S
Gestational age:					
<39 week	8.78 ± 1.85	10.16 ± 2.08	-2.882	0.018	S
≥ 39 week	8.94 ± 1.59	9.41 ± 1.93	-1.436	0.167	NS
Weight:					
2.5 - <3 kg	8.9 ± 1.98	9.28 ± 1.98	-1.011	0.334	NS
3 - <3.5 kg	8.82 ± 1.53	9.59 ± 1.84	-1.484	0.169	NS
3.5 kg-	8.97 ± 1.43	10.4 ± 2.26	-2.626	0.039	NS
Delivery:					
NVD	9.39 ± 1.61	10.11 ± 2.12	-1.697	0.124	NS
CS	8.64 ± 1.65	9.43 ± 1.92	-2.195	0.041	S
Total bilirubin (mg/dl) :					
<16	8.6±1.8	9.9±2	-2.33	0.059	NS
16 - <17	8.68±2.03	8.68±1.7	0	1	NS
17 - <18	8.71±1.98	9.36±2.15	-1.184	0.281	NS
≥18	9.33±1.26	10.13±2.08	-1.742	0.116	NS

There was statistically significant decrease in calcium/creatinine ratio after phototherapy in patients delivered by cesarean section. On the other hand, there was statistically non-significant change in it as regards genders, different age groups, gestational age, weight and level of bilirubin (Table 4).

Table (4): Comparison between calcium/creatinine ratio levels before and after therapy in relation to demographic and clinical data of the studied patients

	Calcium/creatinine ratio				
	Before	After	Z	P	Sig
	Mean ± SD	Mean ± SD			
Gender:					
Male	0.5 ± 0.19	0.43 ± 0.10	-0.758	0.449	NS
Female	0.46 ± 0.10	0.41 ± 0.10	-0.784	0.433	NS
Age:					
2-5 days	0.48 ±0.11	0.43±0.10	-0.341	0.733	NS
6-7 days	0.52 ± 0.12	0.5 ± 0.10	-0.210	0.833	NS
≥ 8 days	0.46 ± 0.11	0.35 ± 0.01	-1.12	0.263	NS
Gestational age:					
<39 week	0.42 ± 0.11	0.47 ± 0.10	-1.129	0.259	NS
≥ 39 week	0.51 ± 0.11	0.4 ± 0.10	-1.793	0.073	NS
Weight:					
2.5 - <3 kg	0.41 ± 0.10	0.41 ± 0.10	-0.549	0.583	NS
3 - <3.5 kg	0.5 ± 0.11	0.41 ± 0.10	-1.682	0.093	NS
3.5 kg-	0.58 ± 0.10	0.46 ± 0.10	-0.676	0.499	NS
Delivery:					
NVD	0.46 ± 0.10	0.51 ± 0.11	-1.070	0.285	NS
CS	0.5 ± 0.11	0.38 ± 0.01	-1.993	0.046	S
Total bilirubin (mg/dl) :					
<16	0.42±0.10	0.45±0.10	-0.563	0.58	NS
16 - <17	0.44±0.11	0.46±0.10	-0.184	0.85	NS
17 - <18	0.48±0.11	0.3±0.01	-1.35	0.176	NS
≥18	0.56±0.10	0.47±0.10	-1.12	0.262	NS

There was statistically non-significant positive correlation between percent change in either urine or serum calcium and any of the above-mentioned parameters. Additionally, there was statistically significant negative correlation between percent change in calcium creatinine ratio after phototherapy and hematocrit level in the studied patients.

Moreover, there was a statistically highly significant negative correlation between percent change in calcium creatinine ratio after phototherapy and percent change in urinary creatinine ratio in the studied patients (Table 5 and figures 2 & 3).

Table (5): Correlation between percent change in serum and urine calcium before and after phototherapy and both clinical and laboratory data

	Percent change in			
	Urine calcium		Serum calcium	
	R	p	R	P
Height	-0.291	0.118	-0.290	0.112
Head circumference	0.182	0.334	-0.161	0.395
Hemoglobin	0.190	0.315	-0.13	0.495
Hematocrit	0.182	0.334	-0.161	0.395
Reticulocytes	-0.149	0.433	0.246	0.190
%change in serum calcium	-0.189	0.317	1	
%change in urine calcium	1		-0.189	0.317
%change in serum creatinine	-0.161	0.396	0.344	0.063
%change in urinary creatinine	-0.016	0.934	0.006	0.975
% change in total bilirubin	0.115	0.544	-0.216	0.251
% change in Direct bilirubin	0.079	0.679	0.197	0.297
% change in urine sodium	0.074	0.697	-0.229	0.224
%change in serum sodium	0.323	0.081	0.042	0.827
%change in calcium/creatinine ratio	0.256	0.172	0.073	0.7
%change in fractional excretion of sodium	0.042	0.827	-0.04	0.835

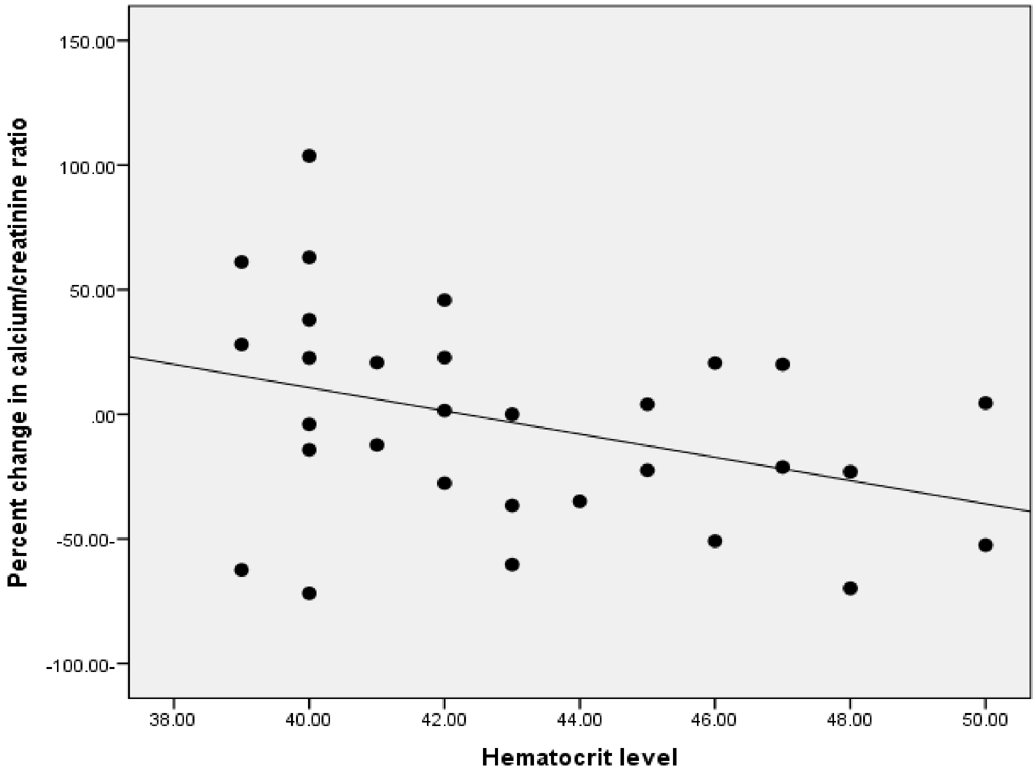

Figure (2): Scatter dot graph showing a statistically significant negative correlation between percent change in calcium creatinine ratio (after phototherapy) and hematocrit level in the studied patients.

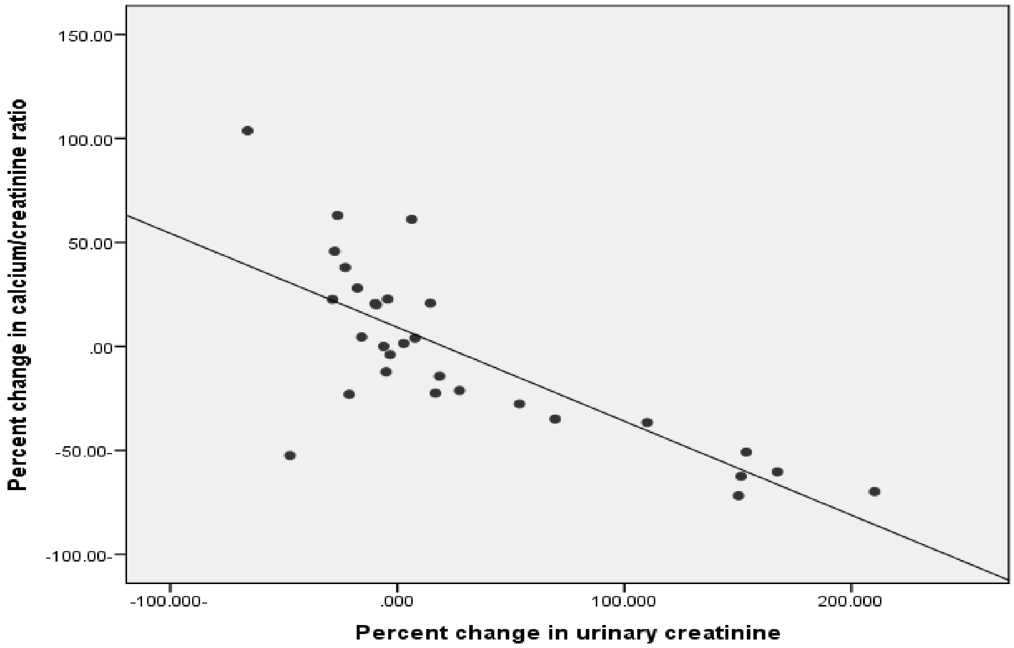

Figure (3): Scatter dot graph showing a statistically significant negative correlation between percent change in calcium creatinine ratio (after phototherapy) and percent change in urinary creatinine in the studied patients.

On stepwise linear regression for factors significantly correlated with percent change in calcium creatinine ratio, it was found that percent change in urine calcium and hematocrit levels independently predict it by β = -0.441 (p<0.001**) and β = - 4.129 (p = 0.006) respectively (Table 6).

Table (6): Linear stepwise regression analysis for factors independently associated with percent change in calcium/creatinine ratio after phototherapy

	Unstandardized coefficients		Standardized coefficient	T	p
	B	Standard error	B		
%change in urinary creatinine	**-0.441**	**0.064**	**-0.741**	**-6.835**	**<0.001****
Hematocrit level	**-4.129**	**1.372**	**-0.326**	**-3.009**	**0.006***

DISCUSSION

Hyperbilirubinemia is largely preventable and treatable by phototherapy. One of phototherapy's main benefits is that it cuts down on the need for transfusion exchange. Hyperthermia, feed intolerance, loose stools, skin rashes, bronze baby syndrome, retinal abnormalities, dehydration, redistribution of blood flow, and genotoxicity are all possible side effects of phototherapy [12]**.** Only a small number of studies have shown that phototherapy can have a negative impact on serum calcium and sodium levels, in contrast to other potential side effects.

Our research looked at how phototherapy affects the levels of calcium and sodium in newborns' blood and how much of each is excreted in their urine. Our study included 30 term neonates, 18 of them (60%) males and 12 of them (40%) female. Their ages range from 2 to 12 days with means of 5.9 ± 2.77 days. Our results showed that two thirds of the studied patients were delivered by CS route while the other third by NVD. Also, two thirds of the studied patients born at gestational age of 39 weeks or more while the other third born before the 39th week. The mean gestational age for the studied patients was 38.9 ± 0.92, the mean weight (kg) was 3.11 ± 0.42, the mean length (cm) was 50.87 ± 2.08, and the mean head circumference (cm) was 34.85 ± 0.62. Similarly, results of **Shahriarpanah** ***et al.*** [13], who studied the effect of phototherapy on serum calcium, magnesium and vitamin D on 50 term infants of them 27 were males (%54) and 23 were females (46%). They showed that the mean of calendar age of the population under the study was 5.52 ± 2.45 days, with the youngest being two days old and the oldest 14 days, and the mean weight during the hospital stay was 3177.4 ± 373.62 g.

Our study revealed that the mean of TSB was 16.67 ± 1.41 mg/dl before phototherapy, while it was 12.23 ± 1.36 mg/dl after phototherapy so there was statistically significant decrease of TSB after phototherapy with median percent decline of 26.67%. This in agreement with **Suneja** ***et al.*** [14] where they found that serum bilirubin levels dropped significantly after phototherapy.

Our study results showed that the mean of serum calcium was 9.74 ± 0.89 mg/dL before phototherapy and 9.64 ± 0.93 mg/dL after phototherapy, with a median percent decline of 1.13% however, this decline was statistically non-significant (the least level of serum Ca post phototherapy was 8.71mg/dl). This is in agreement with **Karamifar *et al.*** [15] who documented that there was decline in serum calcium after exposure to phototherapy, but this decline wasn't statistically significant. **Karamifar *et al.*** [15] attributed this result to short duration of exposure to phototherapy (2 days). In contrary to our results, **Shahriarpanah *et al.*** [13] detected significant decline in serum calcium after exposure to phototherapy. This disagreement could be explained by duration of exposure to phototherapy and the difference in phototherapy type being continuous or extensive.

Our results revealed that there was statistically significant increase in urinary calcium after phototherapy with a median percent increment in urinary calcium of 8.76%. This agrees with **Asl *et al.*** [8] who stated that there was statistically significant increment in urinary calcium in neonates with jaundice underwent phototherapy. Also, **Hooman & Honarpisheh** [7] demonstrated that the urinary calcium level in neonates with jaundice treated by phototherapy was considered higher than that before phototherapy. They attributed the increment in urine calcium excretion to increased vasoactive intestinal peptides (VIP) in infants under phototherapy that leads to intestinal water and electrolyte secretion. VIP leads to increase in renal vascular resistance and FeNa. Reabsorption of calcium in the proximal tubule and loop of Henle is sodium dependent.

Female individuals and patients older than 8 days showed a statistically significant increase in urine calcium after phototherapy. In comparison with **Asl *et al.*** [8] After receiving phototherapy, both sexes showed a statistically significant reduction in their urine Ca levels. In addition, the ratio of urine excretion before and after phototherapy was quite different in infants aged 2–5 days and 8 days. On the other hand, in our study, there was statistically non-significant change in urinary calcium after phototherapy in relation to body weight. This is in contrast with **Asl *et al.*** [8] who found that urinary calcium excretion is increased in neonates weigh 3000 - 3999 gm however, no significant change in those weighs 2500 – 2999 gm.

Our results showed that urinary calcium excretion was increased in neonate born at gestational age less than 39 weeks and in those delivered by CS. **Aladangady *et al.*** [16] stated that urine calcium excretion in the first week of life is correlated inversely with gestational age regardless exposure to phototherapy. Phototherapy may augment this relation.

Concerning calcium/creatinine ratio in our results, the mean was 0.48 ± 0.18 and 0.42 ± 0.19 before and after phototherapy respectively, with a median percent decline of 2%, thus there was statistically non-significant difference in Ca/Cr ratio after phototherapy. This explains why our cases did not enter in hypocalcemia after phototherapy as Ca/Cr ratio did not reach to the level of hypercalciuria (> 0.85). In concordance with our results, **Asl *et al.*** [8] stated that no significant difference was found between urinary Ca/Cr ratio after phototherapy. In contrast, **Imani *et al.*** [17] showed that in neonates with jaundice, calcium/creatinine ratio was 0.28 ± 0.21 and 0.40 ± 0.34 before and after phototherapy respectively. In this regard, calcium/creatinine ratio showed statistically significant increase as in their study where about 13% of their cases had hypercalcuria with Ca/Cr ratio > 0.85.

More than 4 milligrams of calcium is excreted in urine per kilogram of body weight per 24 hours, a threshold above which is considered hypercalciuria. Due to the difficulty in obtaining 24-hour urine samples, the urinary calcium/creatinine ratio in random urine samples has replaced the measurement of calcium excreted per day. This ratio has been shown to closely correlate with 24-hour calcium excretion in adults, healthy children, and children with urolithiasis [8].

Our study revealed that there was statistically significant decrease of calcium/creatinine ratio after phototherapy in patients delivered by cesarean section. On the other hand, there was statistically non-significant change in it after phototherapy in regard to gender, different age groups, gestational age, level of bilirubin and weight. Similarly, **Asl *et al.*** [8] found that urinary calcium /creatinine ratios after phototherapy did not differ significantly with respect to sex, age, gestational age, weight at birth, and total bilirubin levels.

There was statistically significant negative correlation between percent change in calcium /creatinine ratio (after phototherapy) and both hematocrit level and percent change in urinary creatinine in the studied patients. **Hooman & Honarpisheh** [7] stated that hypercalciuria was mainly observed in preterm neonates and no significant relationship was noticed among hypercalciuria and age, sexual orientation, weight, bilirubin level, serum calcium, and urine osmolality, however hematocrit level and percent change in urinary creatinine not assessed.

CONCLUSION

Phototherapy is an effective therapy for neonatal hyperbilirubinemia. Despite presence of an increment in urinary calcium excretion after phototherapy, no significant difference was found in calcium/creatinine ratio after phototherapy, so no hypercalciuria to be considered and in turn it cannot cause hypocalcemia. Phototherapy is neutral regarding renal function and increase calcium excretion is not related to renal dysfunction.

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