Neonatal hypocalcemia and its relation to vitamin D and calcium supplementation

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ABSTRACT

الأهداف: تقييم انتشار نقص معدل كالسيوم الدم في حديثي الولادة لمرضى العيادات الخارجية وعلاقته بفيتامين (D) ومكملات الكالسيوم.

الطريقة: أجريت هذه الدراسة التحليلية المستعرضة في مستشفى الجامعة التعليمي في الفترة من مايو إلى أكتوبر 2016م. وجمعت البيانات من 100 حديثي الولادة عن طريق إجراء مقابلات مع الأمهات باستخدام استبيان ؛ والتي تضمنت معلومات اجتماعية – ديمغرافية وتاريخ مرضي للأمهات والمواليد؛ بالإضافة إلى قياس نسبة الكالسيوم الكلي والمؤين ومستوى فيتامين D بالدم.

النتائج: 76% من حديثي الولادة لديهم نقص كالسيوم الدم، في حين أن 52% منهم لديهم نقص كالسيوم الدم في وقت متأخر. 38%كان لديهم نقص فيتامين D. وجد نقص كالسيوم الدم أكثر انتشارا بين حديثي الولادة مع عدم وجود تاريخ من فيتامين ((D 98.7%))، لا يوجد هناك تاريخ من مكملات الكالسيوم الأمهات (57.9%)، في حين كان لديهم تاريخ من اليرقان الوليدي (46.1%) والتي زادت إلى 53.8% مع نقص كالسيوم الدم في وقت متأخر.

الخاتمة: انتشار نقص كالسيوم الدم الوليدي منتشر على نطاق واسع في محافظة الفيوم مع ارتباط كبير مع الأطفال ذوي التاريخ المرضي لليرقان الوليدي، وايضاً بين الأمهات اللاتي لم يتلقوا الكالسيوم وايضاً بين حديثي الولادة اللذين لم يتلقوا المكملات من فيتامين D.

Objectives: To assess the prevalence of hypocalcemia in outpatient clinic neonates and its relation to vitamin D and calcium supplementation.

Methods: This cross-sectional analytical study was conducted at the University Teaching Hospital from May to October 2016. Data were collected from 100 neonates by interviewing mothers using a structured questionnaire; which included socio-demographic information, maternal and neonatal history; in addition to investigations of serum calcium total and ionized and serum vitamin D level.

Results: The prevalence of hypocalcemia was 76%, late hypocalcemia represent 52% of hypocalcemic neonates. The prevalence of hypovitaminosis D was 38%. Hypocalcemia was found more prevalent among neonates with no history of vitamin D supplementation (98.7%), no history of maternal calcium supplementation (57.9%), while they had a history of neonatal jaundice on phototherapy (46.1%) which increased to 53.8% with late hypocalcemia.

Conclusion: Neonatal hypocalcemia is widely prevalent in Fayoum governorate with significant association with a history of neonatal jaundice on phototherapy, not receiving maternal calcium or neonatal vitamin D supplementation.

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Neonatal mortality in Egypt decreased from 16.2/1000 births in 2009 to 12.8/1000 births in 2015, which reflects the improvement in health care services provided to neonates.[1] Egypt develops a comprehensive national nutrition policy as a part of national development policy to guarantee universal

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availability and accessibility to adequate high quality and safe food, and to promote healthy dietary practices for the prevention and control of nutritional disorders; 2 of these disorders are hypocalcemia, and hypovitaminosis D.[2] Hypocalcemia is a common metabolic manifestation in neonates. It is a potentially life-threatening condition, with reported prevalence varying by gestational age, maternal and infant comorbidities, and perinatal factors.[3] Neonatal hypocalcemia is classified according to its onset to early onset which manifests within the first 72 hours of birth and delayed onset after 3 days of birth.[4] Calcium is the most abundant mineral in the human body. Ionized calcium is essential for many biochemical functions.[5] Hypocalcemia is usually asymptomatic disease but may present with lethargy, vomiting, abdominal distension, poor muscle tone, or poor feeding, and irritability.[6] Vitamin D and its metabolites are fat soluble pro-hormones. In addition to their well-known classic function of hemostasis of calcium, magnesium, and phosphorus level, and keeping skeletal integrity, there are non-classical functions which are related to promoting insulin secretion and action, lung development, antibacterial effect, immune regulation and controlling blood pressure.[7] Nutrition status of mothers has a strong effect on fetal development; maternal supplementation of vitamin D and calcium during pregnancy reflects neonatal vitamin D and calcium level.[8,9] Maternal calcium supplementation reduces the risk of preterm birth which is the leading cause of neonatal mortality.[10] The current study aims to assess the prevalence of hypocalcemia in outpatient clinic neonates and assess its relation to vitamin D and calcium supplementation.

Methods. This is a cross-sectional analytical study conducted at the neonatology outpatient clinic of Fayoum University Hospital. It was carried out over a period of 6 months, from May to October 2016. The sample size was calculated using Epi info 7 software based on an expected prevalence of hypocalcemia; around 50% (with 95% confidence interval and precision of 5%) in order to get the maximum sample size.

One hundred neonates (under 28 days old) from total 150 neonates (66.7%) were recruited in the study by systemic random sample, through choosing every third eligible neonate.

Inclusion criteria. Neonates under 28 days of life seek neonatology outpatient clinic medical care.

Exclusion criteria. No congenital anomalies, no medications, no metabolic syndromes.

Data collection. Data were collected by interviewing mothers using a pre-prepared and pretested structured Arabic questionnaire which included the following 3 sections: the first section introduces sociodemographic information including age, gender, and residence. The second section discusses maternal history including mode of delivery, maternal chronic disease, perinatal maternal complications, and calcium supplementation during pregnancy. The third section discusses neonatal history including gestational age, birth weight, neonatal complications, type of feeding, symptoms of hypocalcemia or other associated symptoms and vitamin D supplementation.

A full general examination was done with special emphasis on CNS examination. Serum ionized, total calcium level and Serum 25 Hydroxy vitamin D level were investigated in all neonates. In the current study, neonatal hypocalcemia is defined by total serum calcium below 8.8 mg/dl (2.2 mmol/L), and serum ionized calcium below 4.41 mg/dl (1.1 mmol/L), as regards vitamin D hypovitaminosis when serum vitamin D below 30 ng/ml (75 nmol/L), it included vitamin D deficiency (<50nmol/L), and insufficient (50-75nmol/L).

Enzyme Linked Florescent Assay (ELFA) technique mini-VIDAS instrument (Bio Mérieux Company) was used to measure serum 25 Hydroxy vitamin D3 level. The assay principle combines enzyme immunoassay competition methods then final florescent detection. The solid phase receptacle (SPR) and the pipetting device for the assay reagents are ready to use and pre-dispensed in the sealed reagent strips. All these steps are performed automatically by the instrument. The reaction medium is cycled several times in and out of the SPR. To separate vitamin D from its binding protein, the sample is mixed with pre-treatment reagent. Then collect the pretreated sample and transferred into anti-vitamin D antibody (conjugate) in presence of an alkaline phosphatase (ALP). The vitamin D antigen that presents in the sample coating the interior of the SPR competes in the binding sites present on the anti-vitamin D antibody – ALP conjugate. During the last detection step, the substrate 4-methyl-umbelliferyl phosphate is cycled in and out of the SPR. The conjugate enzyme catalyzes the hydrolysis of this substrate into florescence which could be measured at 450 nm. The intensity of the florescence is inversely proportional to the concentration of vitamin D antigen present in the sample. Finally, results are calculated automatically by the instrument in relation to the calibration curve stored in memory and then printed out.[11]

Data Analysis. The collected data were statistically analyzed using the Statistical Package for the Social

Science (SPSS) software version 18 (SPSS Inc., Chicago, IL, USA). For quantitative data, the mean and standard deviation were calculated. Independent t-test and ANOVA test were used as the tests of significance. For qualitative data, the number and percent distribution were calculated and chi-square ($\chi 2$) was used as a test of significance. Bivariate person correlation test was used to test the association between quantitative variables. For interpretation of results of tests of significance, significance was adopted at $p \leq 0.05$.

Ethical consideration. This study was approved by the Research Ethical Committee in the Faculty of Medicine, Fayoum University. The study follows the principles of Helsinki Declaration. Verbal consents were obtained from all participants in the study. The confidentiality of their information was confirmed and their right not to participate or withdraw from the study was ensured.

Results. Neonates included in the current study had a mean age of (9.5±8.1) days, and mean birth weight of (2.8±0.50) kg. In the study group, 56% were males and 44% were females. As for the gestational age, 88% of them were full term and 12% were preterm. With regards to the feeding types, 69% of the neonates were being breastfed, while 22% were being formula fed, only 9% depended on combined feeding.

More than half of the study group (56%) were delivered by caesarian section, and 44% by normal vaginal delivery. Only 12% underwent perinatal complications, with 9% premature rupture of membranes (PROM), 1% pre-eclampsia, and 2% with a history of asphyxia.

With regards to the mother illness, only 7% had an illness in the form of the following: 4% hypertension, 2% diabetes mellitus, and 1% nutritional hypocalcemia.

Half of the infants included in the study suffer associated symptoms: 38% had jaundice and receive phototherapy, 1% show hypoglycemia, 1% had a convulsion, 7% for respiratory distress and 3% mixed symptoms (case of jaundice with hypoglycemia, the case of jaundice with respiratory distress (RD), and finally case of RD with hypoglycemia).

The prevalence of neonatal hypocalcemia among a sample of 100 neonates included in the current study was 76%. Among them, 24 (31.6 %) had early hypocalcemia, and 52 (68.4%) had late hypocalcemia.

The mean ionized calcium among the study group was (0.95±0.19) mmol/L, and mean serum total calcium was (7.8±1.31) mg/dl. The mean Serum vitamin D level was (73.7±22.6) nmol/L. Hypovitaminosis of vitamin D (<75 nmol/L) represent 38% of the study group, 14% were deficient (<50 nmol/L), and 24% were insufficient (50-75 nmol/L), the statistically significant high percentage of hypovitaminosis among urban inhabitant neonates with a p=0.02.

Almost half of the mothers (51%) took calcium supplementation during the antenatal period and 8% of the neonates had a history of vitamin D supplementation.

There was a statistically significant high prevalence of neonatal hypocalcemia among neonates who had a positive history of neonatal jaundice on phototherapy (p=0.04), and had not received vitamin D supplementation (p<0.001) and whose mothers had not received calcium supplementation (p=0.002). On the other hand, there was no statistically significance association with other neonatal factors (sex, gestational age, type of feeding, perinatal complication, and vitamin D level) and maternal factors (residence, mode of delivery, and mother illness). (**Table 1**)

There was a statistically significant association between late neonatal hypocalcemia and a positive history of phototherapy with a p-value of 0.04. On the other hand, there was no statistically significant association with other neonatal and maternal factors. (**Table 2**)

There was a statistically significant low mean of serum ionized and total calcium level among neonates whose mothers do not take supplements, and also among neonates with positive history of phototherapy. Additionally, there was a statistically significant association between preterm and low level of neonatal serum vitamin D (p=0.013).

On the other hand, there was no statistically significant association/ statistical association between serum calcium levels and residence, sex, gestational age, type of feeding, mode of delivery, perinatal complication and maternal illness. There was also no statistically significant association/ statistical association between serum vitamin D level and demographic characters (residence, and gender), neonatal and maternal factors. (**Table 3**)

There was a statistically significant positive correlation between total and ionized serum calcium level (r=0.25, p=0.01) and the age of the neonates (r=0.24, p=0.01), which indicated an improvement in total and ionized serum calcium level with age. Similarly, there was a statistically significant positive correlation between serum vitamin D level and birth weight (r=0.23, p=0.02), which indicated that an increase in neonatal serum vitamin D level will be associated with an increase in birth weight.

Discussion. Data on the incidence and prevalence rates of hypocalcemia in the neonatal period are

Table 1 - Association between hypocalcemia and risk factors.

Variables	Normal (n=24)		Hypocalcemia (n=76)		*P*-value
Residence					
Urban	6	(25.0)	14	(18.4)	0.6
Rural	18	(75.0)	62	(81.6)	
Gender					
Males	16	(66.7)	40	(52.6)	0.24
Female	8	(33.3)	36	(47.4)	
Gestational age					
Full term	21	(87.5)	67	(88.2)	0.9
Preterm	3	(12.5)	9	(11.8)	
Type of infant feeding					
Breast	15	(62.5)	54	(71.1)	0.62
Formula	7	(29.2)	15	(19.7)	
Combined	2	(8.3)	7	(9.2)	
Mode of delivery					
Vaginal	12	(50.0)	32	(42.1)	0.78
Caesarian section	12	(50.0)	44	(47.9)	
Perinatal complications					
No	21	(87.5)	67	(88.2)	0.16
Yes	3	(12.5)	9	(11.8)	
Mother illness					
No	22	(91.7)	71	(93.4)	0.16
Yes	2	(8.3)	5	(6.6)	
Associated jaundice					
No	21	(77.5)	41	(63.9)	0.04*
Jaundice	3	(12.5)	35	(46.1)	
Neonatal vitamin D supplement					
Yes	7	(29.2)	1	(1.3)	<0.001*
No	17	(70.8)	75	(98.7)	
Mother calcium supplement					
Yes	19	(79.2)	32	(42.1)	0.002*
No	5	(20.8)	44	(57.9)	
Vitamin D level					
Deficient & Insufficient	12	(50.0)	26	(34.2)	0.23
Sufficient	12	(50.0)	50	(65.8)	

Values are presented as number and percentage (%),
*Statistical significant ($p \leq 0.05$)

Table 2 - Association between different risk factors and time of hypocalcemia.

Variables	Hypocalcemia				*P*-value
	Early (n=24)		Late (n=52)		
Residence					
Urban	6	(25.0)	14	(18.4)	0.33
Rural	18	(75.0)	62	(81.6)	
Gender					
Males	15	(62.5)	25	(48.1)	0.32
Female	9	(37.5)	27	(51.9)	
Gestational age					
Full term	23	(95.8)	44	(84.6)	0.25
Preterm	1	(4.2)	8	(15.4)	
Type of infant feeding					
Breast	17	(70.8)	37	(71.2)	0.09
Formula	7	(29.2)	8	(15.4)	
Combined	0	(0)	7	(13.5)	
Mode of delivery					
Vaginal	11	(45.8)	21	(40.4)	0.80
Caesarian section	13	(54.2)	31	(59.6)	
Perinatal complications					
No	23	(95.8)	44	(84.6)	0.55
Yes	1	(4.2)	8	(15.4)	
Mother illness					
No	21	(87.5)	50	(96.2)	0.16
Yes	3	(12.5)	2	(3.8)	
Associated jaundice					
No	17	(70.8)	24	(46.2)	0.04*
Jaundice	7	(29.2)	28	(53.8)	
Neonatal vitamin D supplement					
Yes	0	(0)	1	(1.9)	0.99
No	24	(100)	51	(98.1)	
Mother calcium supplement					
Yes	11	(45.8)	21	(40.4)	0.80
No	13	(54.2)	31	(59.6)	
Vitamin D level					
Deficient &Insufficient	8	(33.3)	18	(34.6)	0.90
Sufficient	16	(66.7)	34	(65.4)	

Values are presented as number and percentage (%),
*Statistical significant ($p \leq 0.05$)

limited.[12] This study is of value because we included symptomatic and asymptomatic hypocalcemia neonates and provided some new predictors as supplementations to clinicians, which may explain the mechanisms of neonatal hypocalcemia and hypovitaminosis D. The current study revealed that the prevalence of neonatal hypocalcemia was 76%. These results are in agreement with an Iranian study that reported that 100% of neonates included in the study had neonatal hypocalcemia; The percentage of hypocalcaemia in two studies in Kenya and one in Yemen were much lower if compared to our results (21.5%, 34%, and 17.8% respectively).[4,13-15]

Late hypocalcemia was more frequent (68.4%) than early hypocalcemia (31.6 %) in the current study. This result is in agreement with a study conducted in Qatar with 97% late hypocalcemia. These results were not in consistence with other studies in India and Iran

Table 3 - Association between serum calcium and vitamin D in maternal and neonatal risk factors.

Variables	Serum calcium						Serum vitamin D (nmol/L)		
	Ionized (mmol/L)			Total (mg/dl)					
	Mean	SD	*p*-value	Mean	SD	*p*-value	Mean	SD	*p*-value
Residence									
Urban	1.03	0.20	0.06	8.3	1.6	0.08	65.7	27.3	0.07
Rural	0.94	0.19		7.7	1.2		75.7	20.9	
Gender									
Males	0.96	0.22	0.84	7.9	1.4	0.63	71.7	24.4	0.32
Female	0.96	0.16		7.7	1.2		76.3	19.9	
Gestational age									
Full term	0.96	0.19	0.15	7.9	1.3	0.16	75.8	20.9	0.013*
Preterm	0.89	0.18		7.3	1.2		58.6	28.7	
Type of infant feeding									
Breast	0.94	0.18		7.7	1.2		76	22.4	
Formula	0.98	0.19	0.57	7.9	1.5	0.56	70.1	24.1	0.26
Combined	0.99	0.24		8.1	1.8		64.7	18.6	
Mode of delivery									
Vaginal	0.98	0.18	0.17	7.9	1.3	0.18	73.8	23.5	0.94
Caesarian section	0.94	0.19		7.6	1.3		73.6	22	
Perinatal complications									
No	0.96	0.19	0.59	7.8	1.3	0.55	74.9	21.6	0.13
Yes	0.93	0.22		7.6	1.6		64.4	27.9	
Mother illness									
No	0.96	0.19	0.91	7.8	1.3	0.90	74	21.8	0.57
Yes	0.97	0.18		7.7	1.5		69	32.2	
Associated jaundice									
No	1.01	0.18	0.001*	8.1	1.4	0.001*	73.9	22.7	0.91
Jaundice	0.88	0.17		7.3	0.96		73.3	22.6	
Mother calcium supplement									
Yes	1.01	0.20	0.003*	8.18	1.52	0.002*	75.9	27.7	0.06
No	0.90	0.16		7.39	0.89		79.1	29.4	
Neonatal vitamin D supplement									
Yes	1.16	0.13	0.002*	9.28	1.05	0.001*	63.8	27	0.20
No	0.94	0.18		7.67	1.26		78.7	28.4	

*Statistical significant (*p*-value≤ 0.05)

which reported that early hypocalcemia was more frequent than late hypocalcemia.[5,16,17] The prevalence of hypovitaminosis D (<75 nmol/L) in the current study was 38%; in contrast, an Iranian study reported a prevalence of 85%, 90% in an Indian study and 83% in Polish.[13,18,19] This low prevalence in our study is as 80% of mothers were inhabitant rural areas; they depend in their nutrition on butter, eggs, milk, and cheese which are rich in calcium and vitamin D, they are also exposed to the sun during the majority of the day in the field. In addition to the implementation of the American Academy of pediatrics recommendation of vitamin D supplementation (400 IU/day) to neonates since birth till 2 years of age. Endocrine Society recommends vitamin D levels of 30 ng/ml (50 nmol/L), but to guarantee sufficiency and because of the vagaries of some of the assays, the recommended level is between 40 and 60 ng/mL for both children and adults.[20] That means we also had another 45% of neonates who need to take supplementations, as 83% of the study group were less than 40 ng/ml (100 nmol/L). The current study found a statistically significant high prevalence of neonatal hypocalcemia among neonates who do not receive vitamin D supplementation. This result was in agreement with studies conducted in Iran and Bangladesh.[17,21] Additionally, our study revealed a high prevalence of

neonatal hypocalcemia among neonates whose mothers had not received calcium supplementation during pregnancy. Results were in consistence with studies conducted in Algeria, and Korea which revealed that vitamin D and calcium supplementation could prevent neonatal hypocalcemia.[8,22] A study conducted in Kenya found high prevalence of hypocalcemia in infants who had vitamin D deficiency and born to mothers who had both calcium and vitamin D deficiency in their diet.[14] In Korea they reported that maternal vitamin D insufficiency could be associated with the occurrence of late-onset hypocalcemia. Additionally, exclusive breastfeeding without vitamin D supplementation is another risk factor for vitamin D and calcium deficiency in neonates.[23] In Iran, they revealed that all neonates with delayed hypocalcemia were born to mothers with vitamin D deficiency.[17] Unfortunately in our country there is no national policy according to vitamin D intake for pregnant women, but we do have for calcium intake. Reserves of vitamin D in neonates are related to maternal vitamin D supply. So vitamin D deficiency in mothers will reduce placental vitamin D transmission and cause neonate deficiency.[8] In Switzerland, they reported Maternal Vitamin D level during pregnancy has an important effect on the fetus as its effects on the maternal stores for its growth and development.[9] This study illustrated the association between late neonatal hypocalcemia and neonatal jaundice on phototherapy. This finding was in agreement with studies in Pakistan and Iran that reported neonates developed hypocalcemia after receiving phototherapy as a treatment for neonatal jaundice.[24,25] It is similar to an Egyptian which found that hypocalcemia was a complication of phototherapy in newborns.[26] Also, there is a statistically significant association between preterm and low level of serum vitamin D, which is in contrast with a study conducted in Turkey which reported that preterm was associated with hypocalcemia, not with vitamin D deficiency.[27] Our results are consistent with reports of Tunisia, Columbus, Mediterranean region and Samsun; Turkey studies show a higher risk of vitamin D deficiency in less mature neonates.[28-31] The current study found no association between serum vitamin D level, sex, type of feeding, mode of delivery, perinatal complication and maternal illness, which is inconsistent with studies conducted in Turkey.[3,27]

There was a statistical significant positive correlation between total and ionized serum calcium level and the age of neonates; (r=0.24, p=0.01). It indicated that hypocalcemia improves with age. There was also a statistically significant positive correlation between serum vitamin D level and birth weight (r=0.23, p=0.02). This was similar to results of an Indian study.[6] On the other hand, there was no statistical association between serum calcium levels and sex, residence, gestational age, type of feeding, mode of delivery, perinatal complication and maternal illness. The result of a Korean study was different from ours as it reported a high prevalence of neonatal hypocalcemia among formula-fed neonates.[22] It also disagrees with Indian and Iranian studies which concluded that early and late hypocalcemia were more frequent among mothers with diabetes.[5,17]

Limitations of the study. Authors could not afford the cost of vitamin D calcium axis investigations (parathyroid hormone, vitamin D, phosphorus, and magnesium) as it affects neonatal serum calcium levels. Maternal serum calcium and vitamin D levels were not assessed in this study also, due to financial constraints. We cannot fully present all the factors associated with hypocalcemia. We need further studies to asses these factors.

The current study concluded that Neonatal hypocalcemia is widely prevalent in Fayoum governorate especially late-onset with significant association with neonatal jaundice on phototherapy, no maternal calcium or neonatal vitamin D supplementation. Also there was a high prevalence of hypovitaminosis D among urban inhabitant, and preterm neonates. It recommended the implementation of preventative strategies as an effective public health measure for maternal and neonatal health care programs through: 1) calcium and vitamin D supplementation to mothers during pregnancy and lactation; 2) oral vitamin D supplementation to neonates since birth; 3) Routine investigations of serum calcium as a part of maternal and child health care program for early detection and management of neonatal hypocalcemia; 4) Health education program to raise awareness about healthy and dietary lifestyles.

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