Original Article

Changing trend of neonatal Ca/P/Mg status in a Chinese population

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Background: Calcium (Ca), phosphorus (P), and magnesium (Mg) are essential elements for keeping the body homeostasis. We aimed to investigate the changing trend of serum levels of Ca/P/Mg in neonates.

Methods: We enrolled 82 premature newborns, 173 neonatal sepsis, 50 neonatal hypoglycemia, 254 neonatal jaundice, 43 neonatal haemolytic disease, and 59 healthy controls in our retrospective study. Serum levels of Ca/P/Mg were collected and expressed in quarters. We analysed the association between neonatal disorders and Ca/P/Mg levels (fourth quarter *vs.* first quarter) using binary logistic regression analysis. Smooth curve analysis was performed to analyze the non-linear association between birthweight/procalcitonin (PCT) and Ca/P levels. Threshold effect analysis was also performed to yield the turning point of birthweight/PCT in their associations with Ca/P levels.

Results: Binary logistic regression analyses showed that neonatal haemolytic disease, hypoglycemia, sepsis, jaundice, and prematurity were all significantly associated with the fourth quarter of Ca level ($P<10^{-4}$; $P<10^{-4}$; $P<10^{-4}$; P=0.001; and $P<10^{-4}$, respectively). Neonatal hypoglycemia and prematurity were significantly associated with the fourth quarter of P level (P=0.004; and P=0.003, respectively). Neonatal haemolytic disease, hypoglycemia, sepsis, jaundice and prematurity were not associated with Mg level. Birthweight was significantly associated with Ca level before and after the turning point of 3,220 grams. PCT was significantly associated with Ca level before and after the turning point of 16.8 μg/L. Birthweight was significantly associated with P level before the turning point of 2,990 gram. PCT was significantly associated with P level before the turning points of 3.5 and 34.21 μg/L.

Conclusions: Neonatal disorders demonstrated a decreasing trend of serum Ca/P level. A significantly non-linear association was observed between birthweight/PCT and serum Ca/P levels.

Keywords: Calcium; phosphorus; magnesium; disorders; neonate

Submitted Mar 01, 2023. Accepted for publication Aug 02, 2023. Published online Sep 11, 2023.
doi: 10.21037/tp-23-129
View this article at: https://dx.doi.org/10.21037/tp-23-129

Introduction

Calcium (Ca), phosphorus (P) and magnesium (Mg) are all essential for the growth and development of children (1,2). Ca plays an important role in all vital activities and physiological functions of cells (3). Phosphate controls many processes involved in homeostasis and is also regulated by kidney and bones (4). Mg, the fourth most abundant cation, is the second most prevalent intracellular cation in human tissues (5). Ca, P, and Mg are the major minerals of the skeleton, playing a vital role in skeleton development (6). These elements are also important components of certain enzymes, which participate in a lot of physiological processes (7,8).

On the other hand, Ca, P, and Mg are involved in many cellular function, signal pathways and transduction. In

this sense, the dysregulation of Ca, P and Mg status may be the cause of many disorders. For example, metabolic bone disease was a well-documented complication of prematurity due to the disorder of Ca and P (9). Notably, some disorders, such as tetany and seizures, were likely to occur in the neonatal period (10). On the other hand, neonatal hypocalcemia or hypophosphatemia may induce more injury than that in adult. Based on the harms of the dysregulation of Ca/P/Mg, an in-depth study regarding the changing trend of serum status of Ca, P and Mg in neonatal disorders seems imperative.

A number of common disorders, such as neonatal jaundice, neonatal hypoglycemia, and neonatal sepsis often occur during the neonatal period. It was usually noted the alterations of Ca/P/Mg levels occurred in some of these cases. Currently, premature birth is a well-defined cause of dysregulation of Ca, P and Mg (11). Most fetal bone mineralization occurs in the later stage of fetal development (12). Reduced gestation period leads to the lower mineral stores and increased severity of osteopenia (13). Severe infection may also influence the normal function of parathyroid hormone, which lead to the decrease of serum Ca/P levels. Inflammatory response may affect the cellular homeostasis (14), leading to the disorder of trace elements metabolism. However, we also noted that some term newborns had dysregulation of Ca, P and Mg. Hence, we speculated that certain factors were involved in the Ca/P/Mg dysregulation. The status of Ca/P/Mg may differ among different neonatal groups. To further evaluate the association between various neonatal groups and serum Ca/P/Mg status is of great clinical implications.

With the aim of deep understanding this issue, we decided to perform this retrospective study to clarify the changing trend of serum status of Ca/P/Mg in various common neonatal groups.

We also made a smooth curve analysis regarding the relationship between clinical/inflammatory indexes and Ca/P levels for providing a more specific guiding significance. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-129/rc).

Highlight box

Key findings

- Neonatal disorders demonstrated a decreasing trend of serum Ca/P level. A significantly non-linear association was observed between birthweight/PCT and serum Ca/P levels.

What is known and what is new?

- Ca, P, and Mg are essential elements for keeping the body homeostasis.
- Changes of serum Ca and P levels may be associated with neonatal disorders, birthweight/ PCT may influence the serum levels of Ca and P.

What is the implication, and what should change now?

- More attention should be paid to the serum status of Ca and P in the neonatal disorders. Early intervention of the dysregulation of Ca and P may be helpful for the treatment of neonatal disorders.

Methods

Patient population

The study population were collected from the Pediatrics' Department of Shanghai Sixth People's Hospital from January 2016 to January 2019. The cases were enrolled in terms of the following criteria: (I) neonates aged 1–7 days; (II) newborns did not receive any Ca, P or Mg components before tested; (III) mothers of newborns with systemic diseases that may affect the metabolism of trace elements were excluded. The enrolled cases were classified into the groups of premature newborns, neonatal sepsis, neonatal hypoglycemia, neonatal jaundice, and neonatal haemolytic disease. Age and gender-matched normal controls were recruited. The study was performed retrospectively. We enrolled the participants with the complete set of data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Shanghai Sixth People's Hospital (No. 2018-106). This investigation was performed in the retrospective manner. Hence, the informed consent of guardians of participants was waived. All the enrolled data were de-identified. We performed the anonymous data analysis in the retrospective style.

Data collection

We earnestly extracted the clinical and laboratory findings of the cases and controls from the medical records. Demographic and clinical data were reviewed respectively for age, gender, and birth weight. Laboratory data included serum levels of white procalcitonin (PCT), Ca, P, and Mg. The laboratory parameters were tested within three days after birth. Two authors extracted the data independently to avoid the bias.

Table 1 Baseline characteristics of the enrolled newborns

Neonatal groups	N	Age (days), mean ± SD	Boys
Premature newborns	82	3.4±0.7	51
Neonatal sepsis	173	4.1±0.5	105
Neonatal hypoglycemia	50	3.5±0.5	26
Neonatal jaundice	254	3.7±0.4	135
Neonatal haemolytic disease	43	3.6±0.6	21
Neonatal controls	59	3.5±0.5	28

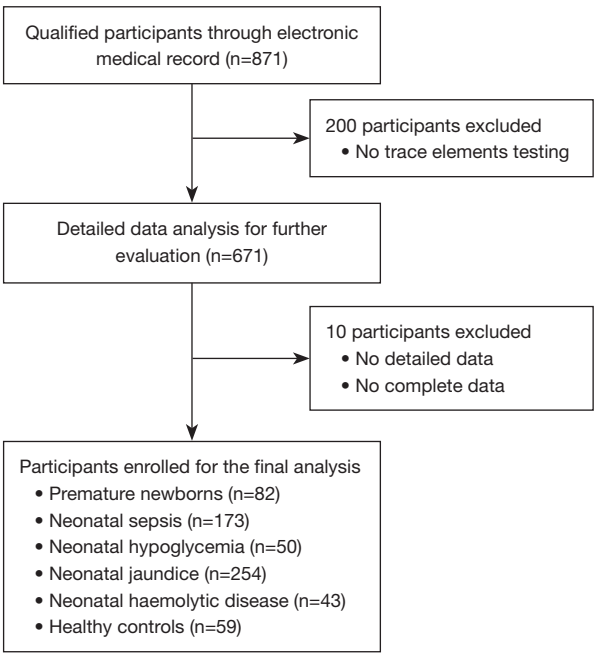

Figure 1 Flow diagram of participants selection.

Statistical analysis

Variables of Ca/P/Mg were grouped in quartiles (0–25%, 25–50%, 50–75%, and 75–100%). Binary logistic regression analysis was applied to test the association between cases of premature newborns/neonatal sepsis/neonatal hypoglycemia/neonatal jaundice/neonatal haemolytic diseases and the fourth quarter of Ca/P/Mg level (75–100%), and the first quarter level of Ca/P/Mg (0–25%) was regarded as the reference. Smooth curve analysis was performed to analyze the non-linear association between birthweight/PCT and Ca/P levels. Threshold effect analysis was also performed to yield the turning point of birthweight/PCT in their associations with Ca/P levels. The P level before and after the turning point was calculated. All the analyses were performed by using R and EmpowerStats software. P<0.05 was considered statistically significant, except where otherwise specified.

Results

Patients characteristics

We collected the neonatal data from the Pediatrics' Department of Shanghai Sixth People's Hospital from January 2016 to January 2019. The neonatal cases involved 82 premature newborns, 173 neonatal sepsis, 50 neonatal hypoglycemia, 254 neonatal jaundice, and 43 neonatal haemolytic disease. 59 healthy controls were also enrolled (*Table 1*). Age and gender were matched between cases and controls (*Table 1*). This study was performed in the retrospective manner. We enrolled the participants with the complete set of data. The flow diagram of participants selection is in *Figure 1*.

Association between neonate and serum Ca/P/Mg level (75–100% vs. 0–25%)

The characteristics of serum Ca/P/Mg status in various neonatal groups are presented in *Table 2*. Binary logistic regression analyses showed that neonatal haemolytic disease, hypoglycemia, sepsis, jaundice, and prematurity were all significantly associated with the fourth quarter of serum Ca level (95% CI: −2.714 to −1.184, $P<10^{-4}$; 95% CI: −2.857 to −1.327, $P<10^{-4}$; 95% CI: −1.875 to −0.738, $P<10^{-4}$; 95% CI: −1.454 to −0.367, P=0.001; and 95% CI: −2.677 to −1.401, $P<10^{-4}$, respectively, *Table 3*, *Figure 2*). Neonatal hypoglycemia and prematurity were significantly associated with the fourth quarter of serum P level (95% CI: −1.982 to −0.379, P=0.004; and 95% CI: −1.686 to −0.342, P=0.003, respectively, *Table 3*, *Figure 3*). Neonatal haemolytic disease, sepsis and jaundice were not associated with serum P level. Neonatal haemolytic disease, hypoglycemia, sepsis, jaundice and

Table 2 Characteristics of Ca/P/Mg status in neonate

Neonatal groups	Ca, mean ± SD	P, mean ± SD	Mg, mean ± SD
Premature newborns	2.195±0.246	1.957±0.305	0.943±0.153
Neonatal sepsis	2.288±0.229	2.033±0.309	0.909±0.092
Neonatal hypoglycemia	2.217±0.236	1.931±0.312	0.902±0.168
Neonatal jaundice	2.326±0.239	2.084±0.288	0.913±0.107
Neonatal haemolytic disease	2.224±0.232	2.147±0.295	0.903±0.092
Neonatal control	2.443±0.159	2.064±0.300	0.899±0.084

Ca, calcium; P, phosphorus; Mg, magnesium.

Table 3 Logistic regression analysis of the association between neonatal disorders and Ca/P/Mg status

Index	OR	95% CI	P
Neonatal haemolytic disease-Ca	−1.949	−2.714, −1.184	$<10^{-4}$
Neonatal hypoglycemia-Ca	−2.092	−2.857, −1.327	$<10^{-4}$
Neonatal sepsis-Ca	−1.306	−1.875, −0.738	$<10^{-4}$
Neonatal jaundice-Ca	−0.910	−1.454, −0.367	0.001
Premature newborns-Ca	−2.039	−2.677, −1.401	$<10^{-4}$
Neonatal haemolytic disease-P	0.305	−0.546, 1.155	0.483
Neonatal hypoglycemia-P	−1.180	−1.982, −0.379	0.004
Neonatal sepsis-P	−0.450	−1.060, 0.159	0.149
Neonatal jaundice-P	−0.102	−0.688, 0.484	0.734
Premature newborns-P	−1.014	−1.686, −0.342	0.003
Neonatal haemolytic disease-Mg	−0.293	−1.164, 0.577	0.509
Neonatal hypoglycemia-Mg	−0.675	−1.473, 0.122	0.098
Neonatal sepsis-Mg	−0.044	−0.679, 0.592	0.892
Neonatal jaundice-Mg	0.001	−0.612, 0.612	1.000
Premature newborns-Mg	0.122	−0.571, 0.816	0.729

Ca, calcium; P, phosphorus; Mg, magnesium; OR, odds ratio; CI, confidence Interval.

prematurity were not associated with serum Mg level (*Table 3*).

Smooth curve analysis of the non-linear association between birthweight/PCT and Ca/P levels

The turning point of birthweight in its association with serum Ca level was 3,220 grams, the p value before and after this turning points was $<10^{-4}$ and 0.002, respectively (*Figure 4*). The first turning point of PCT in its association with serum Ca level was 16.8 μg/L, the P value before and after this turning points was $<10^{-4}$ and 0.039, respectively (*Figure 5*). The first turning point of birthweight in its association with serum P level was 2,990 grams, the P value before and after this turning points was $<10^{-4}$ and 0.377, respectively (*Figure 6*). The first and last turning point of PCT in its association between serum P level was 3.5 and 34.21 μg/L, respectively. The p value before these two turning points was 0.004 and$<10^{-4}$, respectively (*Figure 7*).

Discussion

Ca, P and Mg are significant contributors to bone formation,

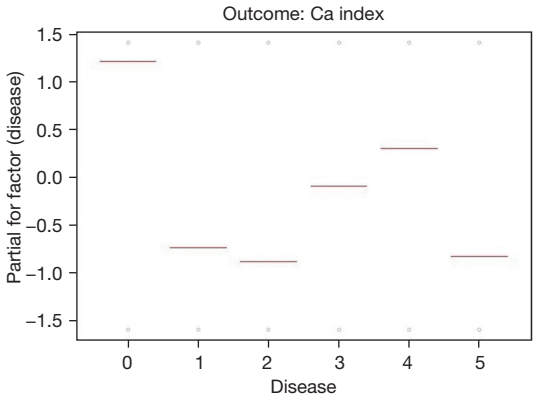

Figure 2 Ca index (Ca level 75–100% *vs.* 0–25%) and neonatal disorders (0: control, 1: hemolytic, 2: hypoglycemia, 3: sepsis, 4: jaundice, 5: premature). Ca, calcium.

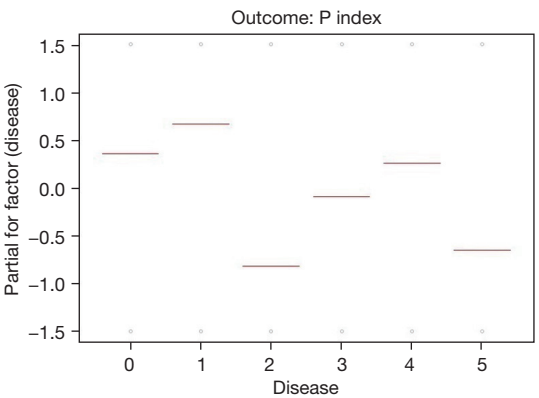

Figure 3 P index (P level 75–100% *vs.* 0–25%) and neonatal disorders (0: control, 1: hemolytic, 2: hypoglycemia, 3: sepsis, 4: jaundice, 5: premature). P, phosphorus.

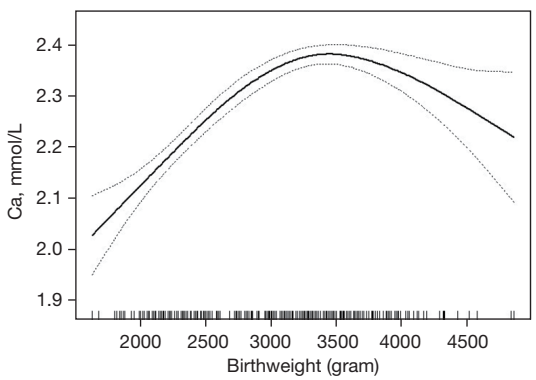

Figure 4 Association between birthweight and Ca status. Ca, calcium

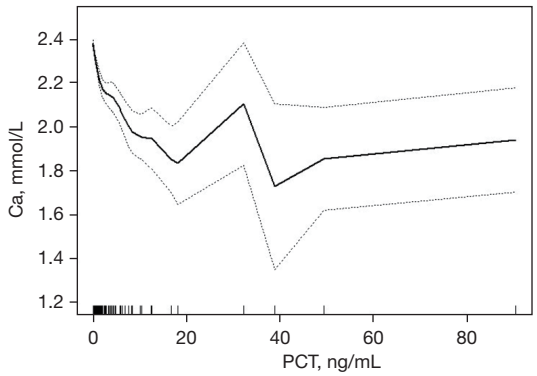

Figure 5 Association between PCT and Ca status. Ca, calcium; PCT, procalcitonin.

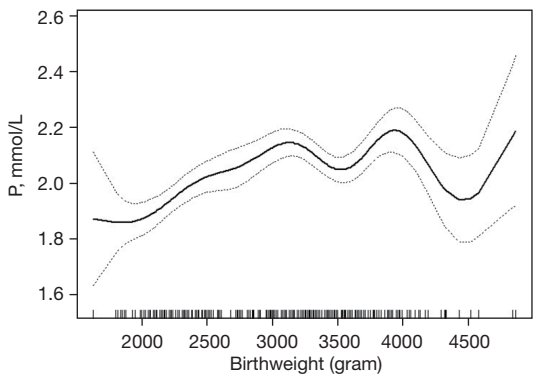

Figure 6 Association between birthweight and P status. P, phosphorus.

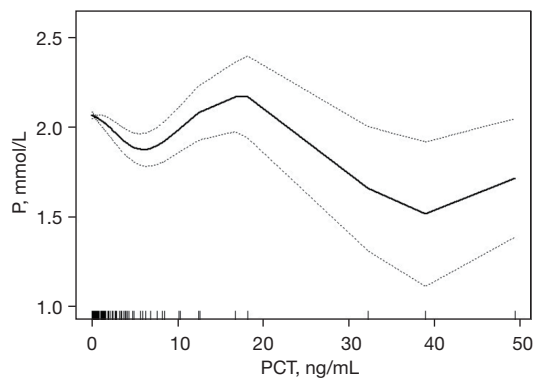

Figure 7 Association between PCT and P status. P, phosphorus; PCT, procalcitonin.

and important components of many enzymes, which play an important role in many physiological processes. Ca, P and Mg participate in many vital signal pathways and transduction in the body. Neonatal hypocalcemic seizures are prone to have worse neurodevelopmental outcomes (15). The long-term antenatal $MgSO_4$ administration affected bone mineralization through the fetal and neonatal period (16). Early parenteral Ca and P supplementation and optimising enteral supplementation with multicomponent fortifiers reduce the incidence of metabolic bone disease (17). Therefore, early detection of Ca/P/Mg seems of great implications. It is also very important to identify infants who are at risk to prevent or treat mineral homeostasis alterations (18).

We performed this study investigating the association between neonate and changing trend of serum Ca/P/Mg status. We also studied the correlation between birthweight/PCT and serum Ca/P status. Our findings indicated that neonatal haemolytic disease, hypoglycemia, sepsis, jaundice, and prematurity were all significantly associated with the fourth quarter of serum Ca level. Neonatal hypoglycemia and prematurity were significantly associated with the fourth quarter of serum P level. A significantly non-linear correlation between birthweight/PCT and serum Ca/P levels was observed. These findings indicated a decreasing trend of serum levels of Ca/P in neonatal disorders, inflammation may affect this trend. Early resolution of these elements disorders may be helpful for treating the specific neonatal disorders.

Several mechanisms may account for our findings. First, fetal Ca and P are supplied primarily during the development stage. Premature delivery and low birthweight decrease the supply of these minerals, leading to the reduced level of Ca/P among premature and low-birthweight newborns. Notably, we found that neonatal disorders did not affect the level of Mg, which may be due to the fact that Mg is the antagonist of Ca (19). Lower level of Ca results in a higher status of Mg. Mg itself is a multivalent cation, important for many biological and cellular functions, including synthesis and nucleotide metabolism (20). Antenatal Mg sulfate intake reduces the risk of death and the inability to walk without assistance (20). On the other hand, Mg administration is likely to be applied in women with premature labour due to its property of decreasing the risk of cerebral palsy (21). We speculate that multiple factors may influence the level of Mg, and further analysis should be performed adjusting for the confounding factors.

Second, intake of Ca was inversely associated with serum C-reactive protein (CRP) level in the general population (22). Activation of Ca-regulated autophagy promoted the killing of mycobacterium (23). Ca could strengthen the phagocytosis of macrophages (24). As a second messenger, Ca also plays an important role in the cellular proliferation and activation, which supports our finding that neonatal sepsis increased the risk of lower level of Ca. Previous study also showed that ionized Ca level was associated with sepsis severity and was a potential independent predictor of poor prognosis in very low birth weight with sepsis (3). Early identification and assessment is very helpful for the prevention and treatment of neonatal sepsis. Notably, sequential organ failure assessment (SOFA), a tool based on the presence of the organ dysfunction, was applied to evaluate the severity of suspected septicemia (25). SOFA can accurately reflect the impact of sepsis on various organs. SOFA score varies across different types of infections (26). SOFA score discrimination to predict mortality was highest among endocarditis (26). SOFA emerges as a potential tool in the definition and prognostication of sepsis.

On the other hand, some other potential biomarkers for sepsis merit attention. For example, presepsin, consisting of the N-terminal 13kDa fragment of the CD14 protein which can transfer the LPS signal from the bacteria via TLR4, leading to a systematic inflammatory response, is a diagnostic biomarker for sepsis in adult and neonates (27). Immunodeficiency was more frequent in cases with increased presepsin levels (28). Patients with higher status of presepsin had a longer duration of infection and a lower incidence of resolution, leading to multi-organ failure (28). Compared with the traditional sepsis markers, such as CRP and PCT, presepsin has higher sensitivity and diagnostic accuracy due to the fact that presepsin levels increase within 2 hours and peak at 3 hours after the onset of infection (29). Interestingly, the presepsin level in the gram-negative bacteria was significantly higher than that in the gram-positive bacteria (30). Presepsin may have different predictive value in the sepsis with various pathogens. Cutoff value of presepin for diagnosing sepsis is different in terms of the clinical settings (29). Previous study showed that cutoff values ranged from 317 to 849 pg/mL and the optimal cutoff value was 600–650 pg/mL in adult (31). Neonatal meta-analysis showed that presepsin cutoff value ranged from 304.5 to 885.0 pg/mL. A cutoff value of >600 ng/L showed higher diagnostic accuracy (32). Cutoff value for detecting pediatric sepsis ranged from 240 to 1,014 pg/mL with an optimal cutoff value of >650 pg/mL (29). Further larger number studies should be performed to

investigate the optimal reference ranges of presepsin for detecting sepsis among different populations.

P is an important component of DNA and ATP, which mainly provides the energy for cell (33). P status imbalances often occur in neonates from clinically insignificant to those that can be life-threatening (34). Hypophosphatemia was reported to be associated with sepsis severity and prognosis (35,36). Hence, lower levels of P may dysregulate the body homeostasis, including the activation of inflammation. PCT is a classic biomarker for inflammatory response. Our findings also indicated a significantly non-linear association between PCT and serum Ca/P status, which suggested that inflammation may affect the status of Ca/P. Of note, we found that serum P status was not associated with sepsis, which may be due to the fact that the sepsis cases included in our study were comparatively mild in symptoms.

Third, we observed that serum Ca/P status was significantly associated with neonatal hypoglycemia, which may be due to the fact that hypoglycemia could result in the decrease of energy production, affecting the cellular metabolism. Hypocalcemia in the neonates may induce the apnea, stridor, and seizures (2,37), which may further influence the appetite, decreasing the serum glucose level. Birth asphyxiated neonates who are likely to be complicated with metabolic disorder were found to have significantly low level of Ca (38). Analysis of the biochemical indexes can help the effective management of birth asphyxia cases (38). Inborn errors of metabolism also include hypophosphatasia.

Finally, we found that serum Ca level was significantly associated with neonatal jaundice and haemolytic disease. The onset of hyperbilirubinemia is due to the excessive erythrocyte damage, which may lower the appetite of newborns. On the other hand, increased meconium and urine excretion may decrease the serum level of Ca. Notably, hypocalcemia is also one of the common adverse effects of phototherapy (39), which may promote the hypocalcemia.

Our study had obvious strengths that: we clarified the association between serum levels of Ca/P/Mg and various neonatal disorders. We also calculated the turning points of birthweight/PCT in their association with Ca/P levels, which provided an important guiding significance, particularly in the clinical practice. These findings had important clinical implications that monitoring and early intervention may be needed in the neonatal disorders. Our findings also give rise to two questions. First, keeping the homeostasis of Ca/P requires the interaction between the kidneys, gastrointestinal systems and bone. Dietary and urine monitoring may be helpful for the evaluation of the impact of other factors on the status of Ca/P. Regrettably, due to the time limit, we did not conduct a follow-up. Further studies should be focused on this issue. Second, the dysregulations of Ca/P levels may alleviate with the remission of neonatal disorders. The optimal time point for intervention remains elusive. It is very helpful for guiding the therapy by clarifying this issue.

In the past, a number of studies were performed to investigate the association between Ca/P/Mg levels and various diseases. Mg was closely with the risk of cardiovascular diseases (40). Decreased level of Mg was linked to the impaired glucose homeostasis, insulin function and inflammation (41). Increased levels of Ca affected the risk of cardiovascular diseases through vascular calcification and coagulability (42). Ca and Mg were negatively associated with lipids profile (43). A higher age and lower BMI were noted among hyphosphatemic patients (44). Hyphosphatemia also indicated a poor clinical outcome (45). All these above-mentioned findings support the idea that Ca/P/Mg dysregulations are likely to induce the damages of multi-organs. Compared with adults, more attention should also be paid to the nutrition intake due to the lower immunity during the neonatal stage. The dysregulation of Ca/P may lead to more adverse outcomes in the newborns. Hence, prompt monitoring and intervention of Ca/P levels during the neonatal stage are of great implications.

Several limitations merit attention in our study. First, the retrospective design might lead to the recall bias, we have to seek the reliable clinical and laboratory data. Second, due to the time limit and loss of follow-up, we did not observe the long-term alterations of serum level of Ca/P/Mg. Finally, a long-term, continuous, lager number of study should be needed in the future to increase the statistical power.

Conclusions

Taken together, our investigation indicated a decreasing trend of serum levels of Ca/P in neonatal disorders, inflammation may affect this changing trend. However, more larger number of studies should be performed to validate our findings.

Acknowledgments

Funding: This study was supported by grant from the National Natural Science Foundation of China (No. 81600578), weak discipline construction of Shanghai health and family planning commission (No. 2016ZB0102-03)

and grant from China Hospital Development Institute of Shanghai Jiao Tong University (No. CHDI-2018-B-06).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-129/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-129/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-129/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Shanghai Sixth People's Hospital (No. 2018-106). This investigation was performed in the retrospective manner. Hence, the informed consent of guardians of participants was waived.

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Cite this article as: Mao S, Wu L, Shi W. Changing trend of neonatal Ca/P/Mg status in a Chinese population. Transl Pediatr 2023;12(9):1659-1667. doi: 10.21037/tp-23-129

