Original Article

Relationship between bronchopulmonary dysplasia, long-term lung function, and vitamin D level at birth in preterm infants

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Background: We aimed to investigate the relationship between the level of serum 25 hydroxyvitamin D [25-(OH)D] at birth and the complications of bronchopulmonary dysplasia (BPD), as well as the long-term lung function of preterm infants.

Methods: A total of 286 premature infants who were admitted to the neonatal ward of Haikou Maternal and Child Health Hospital from January 2018 to December 2020 and met the inclusion criteria were selected as the research objects. The level of serum 25(OH)D at birth was detected. The children were divided into a BPD group (79 cases) and a non-BPD group (207 cases). The case information and basic data of the children were recorded. The children were followed up 6 months after correcting the gestational age of 40 weeks, and their long-term lung function development was reported. Logistic regression analysis was used to evaluate the high-risk factors of BPD in preterm infants.

Results: The 1- and 5-minute Apgar scores of preterm infants in the BPD group were significantly lower than those in the non-BPD group. Also, the combined neonatal pneumonia, neonatal asphyxia, hospital stay, and total oxygen therapy time in the BPD group were substantially higher than those in the non-BPD group. The mean value of serum 25-(OH)D at birth in the BPD group (33.7±15.1 nmol/L) was significantly lower than that in the non-BPD group (49.5±19.6 nmol/L). Compared with the non-BPD group, the respiratory rate (RR) in the BPD group increased significantly, while the tidal volume (VT), inspiratory to expiratory ratio (TI/TE), ratio of time to peak tidal expiratory flow to total expiratory time (TPEF/TE), and 25% tidal expiratory flow rate (TEF25%) decreased markedly ($P<0.05$). Total oxygen therapy time, neonatal pneumonia, neonatal asphyxia, and serum 25-(OH)D level at birth were identified as independent risk factors for BPD in preterm infants.

Conclusions: The level of serum 25-(OH)D in preterm infants at birth is closely related to the occurrence of BPD and long-term lung function damage, and is affected by multiple high-risk factors. This study provides a theoretical basis for the individualized treatment of preterm infants and the early prevention of BPD.

Keywords: Premature infants; 25 hydroxyvitamin D; bronchopulmonary dysplasia (BPD); pulmonary function

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Introduction

With the development of neonatal intensive care technology, the application of pulmonary surfactants, and prenatal glucocorticoids, the survival rate of preterm infants has been significantly improved. However, bronchopulmonary dysplasia (BPD) is one of the most common severe respiratory system complications in preterm infants, especially for small preterm infants. The incidence of BPD in very low birth weight infants can exceed 30% (1,2). Previous studies have shown that the occurrence of BPD can prolong the hospitalization time and increase the complications of preterm infants. In the long term, BPD can easily to lead to recurrent respiratory tract infection, wheezing, lung function damage, psychomotor retardation, and other diseases, which seriously affect the survival rate and quality of life of preterm infants (3). At present, the exact pathogenesis of BPD is still unclear, and increased levels of chemokines, inflammatory cytokines, and proteases caused by pulmonary inflammation can hinder the development and repair of neonatal lungs, and may induce BPD. There remains a lack of effective measures to prevent and treat BPD.

Vitamin D is a sterol hormone. Vitamin D deficiency can easily lead to rickets and metabolic bone diseases, as well as an increased risk of respiratory conditions such as respiratory infection (4) and bronchial asthma (5). In recent years, numerous studies have confirmed that vitamin D has complex biological functions, including the regulation of innate and adaptive immune function, as well as anti-inflammatory and antioxidant effects. Vitamin D also regulates lung development and maturity, and reduces lung injury caused by various factors (6-8). Studies have shown that vitamin D can participate in the synthesis of pulmonary surfactants, and can improve lipopolysaccharide-induced acute lung injury by maintaining the integrity of the alveolar epithelial barrier. In addition, vitamin D supplementation can significantly inhibit lung inflammation and reduce lung damage (6-8). Hence, it is related to the occurrence and development of a variety of lung diseases. In addition, a previous study also found that low serum 25-hydroxyvitamin D [25-(OH) D] level on the first day after birth was an independent risk factor for respiratory distress syndrome (7). Ge *et al.* reported the correlation between vitamin D and vitamin E and the occurrence of BPD, and believed that vitamin D/E deficiency was related to the severity of BPD (9). However, the correlation between vitamin D and long-term lung function in children with BPD is still lacking.

Therefore, this study defined the lung function of children 6 months after the correction of 40 weeks of gestational age as long-term lung function. This study aims to explore the relationship between serum 25(OH)D level at birth and BPD in preterm infants, as well as its impact on long-term lung function, so as to provide new ideas for the clinical prevention and treatment of BPD, and to improve the quality of life of children. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tp-21-494).

Methods

Research objects

Two hundred eighty-six premature infants who were admitted to the neonatal ward of Haikou Maternal and Child Health Hospital from January 2018 to December 2020 and met the inclusion criteria were selected as the research subjects. The inclusion criteria were as follows: (I) infants born in our hospital and transferred to our neonatal ward immediately after birth; (II) those with complete clinical case data; and (III) very low and ultra-low birth weight infants (gestational age <37 weeks, birth weight <1,500 g preterm infants) admitted to the neonatal intensive care unit (NICU) for more than 28 days. The exclusion criteria were as follows: (I) infants with severe congenital malformations, genetic and metabolic diseases, chromosome diseases, or other organ function emergencies; (II) cases where the mother was complicated with severe liver, kidney, and thyroid diseases; (III) cases involving abandonment of treatment or death during hospitalization; and (IV) infants with incomplete personal clinical and laboratory index data. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Haikou Maternal and Child Health Hospital (No. 2017062) and informed consent was obtained from infants' parents.

Object grouping

Firstly, the children were divided into a BPD group (79 cases) and a non-BPD group (207 cases). Any newborn with oxygen dependence (>21%) for more than 28 days established in the fourth edition of practical neonatology was diagnosed with BPD. Secondly, we divided the children into lung function impairment group and non-pulmonary function impairment group according to the long-term lung

function test.

Data collection and processing

The following detailed primary clinical data of all children were collected: (I) data of preterm infants: birth gestational age, gender, weight, Apgar score, complications, days of hospitalization during hospitalization, and total oxygen therapy time; and (II) maternal data: maternal age, mode of delivery, premature rupture of membranes, preeclampsia, gestational diabetes mellitus, and prenatal hormone use.

Determination of serum 25(OH)D level

A total of 2 mL peripheral venous blood samples of all preterm infants and 6 months after 40 weeks of corrected gestational age included in the study were collected. After standing at room temperature for 10–20 min, they were centrifuged at 3,000 r/min at 4 ℃ for 15min with a centrifugation radius of 13.5 cm. After serum separation, the 25-(OH)D level was detected using the chemiluminescence analysis (CLIA) method. Detection was completed using a chemiluminescence immunoanalyzer (SIEMENS, Germany). Serum 25-(OH)D <50 nmol/L was diagnosed as vitamin D deficiency (10).

Pulmonary function measurement

All children included in the study were followed up, and their pulmonary function was measured 6 months after correcting the gestational age of 40 weeks. The long-term pulmonary function of preterm infants was measured by tidal respiratory pulmonary function, and its parameters can sensitively reflect the ventilation dysfunction of children with BPD. Taking the tidal volume per kilogram of body weight (VT/kg) as the index, VT/kg <6 was considered to indicate obstructive ventilation disorder. Other pulmonary function indexes included respiratory rate (RR), respiratory/expiratory ratio (TI/TE), peak time ratio (TPEF/TE), peak volume ratio (VPEF/VE), and expiratory flow rate at 25%/50%/75% tidal volume (TEF 25%/50%/75%).

Statistical analysis

SPSS 22.0 statistical software (IBM, USA) was used for the *t*-test and chi-square test. Multivariate logistic regression was used to analyze the risk factors related to BPD in children. P<0.05 was considered statistically significant.

Results

Comparison of general conditions of children

A total of 286 eligible preterm infants were included in this study, including 79 cases in the BPD group and 207 cases in the non-BPD group. In the BPD group, there were 32 women (40.5%). Also, the average gestational age of infants in this group was 28.9±1.7 weeks, and the average birth weight was 1,139±143.6 g. In the non-BPD group, there were 105 women (50.7%), the average gestational age was 30.3±1.8 weeks, and the average birth weight was 1,281±150.3 g. There were no significant differences in the proportion of females, gestational age, and birth weight between the two groups (P>0.05). Moreover, there were no significant differences in maternal cesarean section rate, premature rupture of membranes, preeclampsia, gestational diabetes mellitus, and antenatal hormone ratio between the two groups (P>0.05). The 1- and 5-minute Apgar scores of preterm infants in the BPD group were markedly lower than those in the non-BPD group. Also, the combined neonatal pneumonia, neonatal asphyxia, hospital stay, and total oxygen therapy time in the BPD group were substantially higher than those in the non-BPD group (P<0.05, *Tables 1,2*).

Comparison of serum 25-(OH)D levels between the two groups

The percentage of vitamin D deficiency at birth was 88.7% (70/79) in the BPD group, which was significantly higher than that of the non-BPD group (70.5%, 146/207), and the difference was statistically significant (P<0.05). The mean values of serum 25-(OH)D at birth were 33.7±15.1 and 49.5±19.6 nmol/L in the BPD and non-BPD groups, respectively. At 6 months after 40 weeks of corrected gestational age, the vitamin D deficiency rate of children in the BPD group was 72.1% (57/79), which was significantly higher than the vitamin D deficiency rate of children in the non-BPD group (43.0%, 89/207) and the difference was statistically significant (P<0.05). The average serum 25-(OH)D of children in the BPD group and non-BPD group were 51.9±16.5 and 66.3±22.1 nmol/L, respectively. The difference between the two groups was statistically significant (P<0.05) (*Table 3* and *Figure 1*).

Long-term pulmonary function comparison between the two groups

On pulmonary function tests, we found that long-term infants in the BPD group had significantly increased RR

Table 1 Comparison of clinical characteristic between premature infants in the BPD and non-BPD groups

Relevant factors	BPD group (n=79)	Non-BPD group (n=207)	t/χ^2	P value
Apgar scores ($\bar{x}$±s, scores)				
1 min	6.4±1.1	7.9±1.1	t=4.312	<0.001
5 min	8.1±1.2	9.1±1.0	t=2.998	<0.001
Hospital stay ($\bar{x}$±s, days)	40.3±13.1	35.2±8.8	t=−2.437	0.032
Total oxygen therapy time ($\bar{x}$±s, days)	32.5±9.3	6.6±1.3	t=−5.238	<0.001
Neonatal pneumonia, n (%)	39 (49.4)	46 (22.2)	χ^2=0.096	<0.001
Neonatal asphyxia, n (%)	23 (29.1)	25 (12.1)	χ^2=0.136	<0.001

P<0.05 was considered statistically significant. BPD, bronchopulmonary dysplasia.

Table 2 Comparison of maternal data and pregnancy complications between the two groups

Relevant factors	BPD group (n=79)	Non-BPD group (n=207)	χ^2	P value
Cesarean section, n (%)	39 (49.4)	87 (42.0)	0.887	0.368
Premature rupture of membranes, n (%)	22 (27.8)	59 (28.5)	1.017	0.695
Preeclampsia, n (%)	8 (10.1)	19 (9.2)	0.968	0.577
Gestational diabetes mellitus, n (%)	20 (25.3)	36 (17.4)	0.086	0.069
Prenatal hormone use, n (%)	43 (54.4)	119 (57.5)	1.009	0.846

P<0.05 was considered statistically significant. BPD, bronchopulmonary dysplasia.

Table 3 Comparison of serum 25-(OH)D level and vitamin D deficiency rate between the two groups

Detection time	Relevant factors	BPD group (n=79)	Non-BPD group (n=207)	t/χ^2	P value
At birth	25-(OH)D ($\bar{x}$±s, nmol/L)	33.7±15.1	49.5±19.6	t=3.435	<0.001
	Vitamin D deficiency, n (%)	70 (88.7)	146 (70.5)	χ^2=0.317	<0.001
6 months after 40 weeks of corrected gestational age	25-(OH)D ($\bar{x}$±s, nmol/L)	51.9±16.5	66.3±22.1	t=5.257	<0.001
	Vitamin D deficiency, n (%)	57 (72.1)	89 (43.0)	χ^2=19.452	<0.001

P<0.05 was statistically significant. BPD, bronchopulmonary dysplasia.

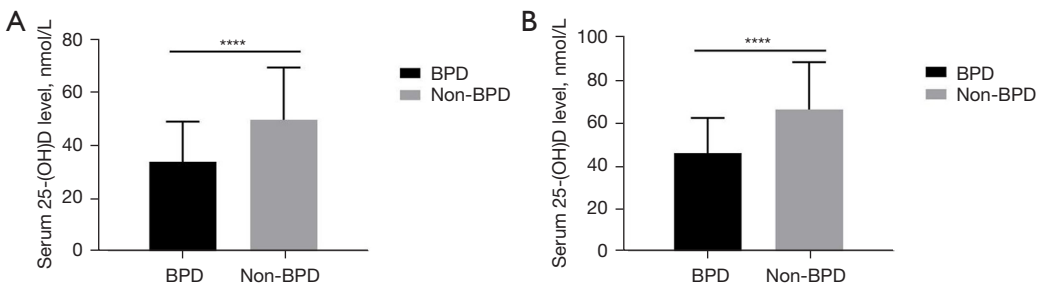

Figure 1 Comparison of serum 25-(OH)D levels between the BPD and non-BPD groups. (A) Serum 25-(OH)D level at birth; (B) serum 25-(OH)D level at 6 months after 40 weeks of corrected gestational age. ****, P<0.0001. BPD, bronchopulmonary dysplasia.

Table 4 Comparison of the long-term lung function between the BPD and non-BPD groups

Relevant factors	BPD group (n=79)	Non-BPD group (n=207)	t/χ^2	P value
RR ($\bar{x}$±s, n/min)	31.5±5.2	29.5±4.6	t=−1.969	0.027
VT ($\bar{x}$±s, mL/kg)	7.2±0.7	8.5±0.6	t=4.387	<0.001
TI/TE ($\bar{x}$±s, %)	72.5±7.0	77.2±8.3	t=3.577	<0.001
TPEF/TE ($\bar{x}$±s, %)	29.4±4.2	33.1±5.6	t=2.611	0.004
VPEF/VE ($\bar{x}$±s, %)	28.9±3.0	29.5±3.3	t=1.332	0.054
TEF 25% ($\bar{x}$±s, mL/s)	53.1±7.1	57.2±7.8	t=3.812	<0.001
TEF 50% ($\bar{x}$±s, mL/s)	66.5±10.5	68.8±11.3	t=1.131	0.077
TEF 75% ($\bar{x}$±s, mL/s)	71.3±12.2	72.8±14.9	t=1.056	0.236
Impairment of lung function (x, %)	63 (79.7)	62 (29.9)	χ^2=57.62	<0.001

P<0.05 was considered statistically significant. BPD, bronchopulmonary dysplasia.

Table 5 Multivariable logistic regression analysis of BPD

Relevant factors	Multivariate logistic analysis		
	OR	95% CI	P
Length of hospital stay	1.08	0.92–1.32	0.068
Total oxygen therapy time	1.33	1.07–3.59	0.003
Neonatal pneumonia	1.25	1.09–1.77	0.022
Neonatal asphyxia	2.33	1.08–4.38	0.029
Serum 25-(OH)D levels	1.46	1.12–1.89	0.013

P<0.05 was considered statistically significant. BPD, bronchopulmonary dysplasia. OR, odds ratio; CI, confidence interval.

and considerably lower VT, TI/TE, TPEF/TE, and TEF 25% compared to those in the non-BPD group, and the differences were statistically significant (P<0.05). There were no notable differences between the two groups in terms of VPEF/VE, TEF 50%, and TEF 75%. The proportion of children with lung function impairment in the BPD group was 79.7% (63/79), which was significantly higher than the proportion of children with lung function impairment in the non-BPD group (29.9%, 62/207). The difference was statistically significant (P<0.05) (*Table 4*).

Logistic regression analysis of risk factors for the development of BPD in preterm infants

Univariate regression analysis was first performed to determine whether BPD occurred as a dependent variable in logistic regression analysis. Independent variable indicators with statistical significance (P<0.05) in the analysis results were included in the multivariate analysis. Finally, the length of hospital stay, total oxygen therapy duration, neonatal pneumonia, neonatal asphyxia, and serum 25-(OH)D level at birth were identified as independent variables in the multivariate logistic regression analysis. The results showed that total oxygen therapy duration, neonatal pneumonia, neonatal asphyxia, and serum 25-(OH)D levels at birth were independent risk factors for the development of BPD in preterm infants (P<0.05, *Table 5*).

Discussion

Although BPD is one of the most common severe complications in preterm infants, its exact pathogenesis remains unclear at present. Children with BPD can present clinically with progressive dyspnea, hypoxemia, etc. Severe cases can develop complications such as pulmonary hypertension and even pulmonary heart disease, primarily due to the pathophysiological changes secondary to the severe lung tissue damage of the affected children, including decreased pulmonary compliance and increased airway resistance dysregulated ventilation/flow ratio. Children with BPD have a poor long-term prognosis. They are prone to recurrent respiratory infections, wheezing, cardiopulmonary impairment, and backward physical development, seriously affecting their quality of life. Recent studies have found that vitamin D has complex biological functions, including the regulation of immune function, anti-inflammation, antioxidation, regulation of lung development and maturation, and alleviation of lung

injury due to various causes. It has also been shown to be closely associated with respiratory infection (11), neonatal respiratory distress syndrome (7), chronic obstructive pulmonary disease (12), and other lung diseases. Therefore, this study aimed to identify the high-risk factors affecting the occurrence of BPD in preterm infants by exploring the relationship between serum 25-(OH)D in preterm infants and the occurrence of BPD and long-term pulmonary function impairment, in the hope of providing new ideas for the early prevention and clinical prevention of BPD.

Vitamin D levels in newborns depend mainly on maternal vitamin D levels and placental transport. Since placental transport of vitamin D occurs primarily in the third trimester, preterm infants can develop insufficient vitamin D reserves. At the same time, preterm infants are highly susceptible to vitamin D deficiency (13) because their intestinal flora is not established, and their intestinal absorptive function is poor. The incidence of vitamin D deficiency in preterm infants in this study (75.5%) is generally consistent with the results reported in previous studies (14,15). At the same time, we found that the mean serum 25-(OH)D of the preterm born BPD group in this study cohort was significantly lower than that of the non-BPD group, and a significantly higher proportion of long-term lung function abnormalities in the BPD group compared to those in the non-BPD group. The above results suggest that vitamin D deficiency at birth may be associated with the occurrence of BPD and long-term lung function impairment.

In recent years, there have been relevant studies exploring the correlation between serum 25-(OH)D levels and the occurrence of BPD in preterm infants. Çetinkaya *et al.* (16) found that serum 25-(OH)D levels at birth were significantly lower in preterm infants in the BPD group than in the non-BPD group in a study of 132 preterm infants ≤32 weeks gestational age. Mao *et al.* (17) reported similar conclusions and indicated that the 25-(OH)D level is an important factor in predicting BPD occurrence. Vitamin D may exert biological functions by acting via the vitamin D receptor on vitamin D pathway genes, many of which regulate lung development (18). Vitamin D may also play a key role in lung maturation by stimulating lung epithelial-mesenchymal cell interactions (19). In addition, studies have found that vitamin D also reduces the synthesis of transforming growth factor-β (TGF-β), matrix metalloprotein (MMP), and tumor necrosis factor (TNF-α) to inhibit airway remodeling (16,17), and can attenuate lung injury caused by hyperoxia (12). The above mechanisms may collectively constitute a relevant link through which vitamin D influences the occurrence of BPD. In the present study, preterm infants in the BPD group had lower serum 25-(OH)D levels at birth than those in the non-BPD group, and serum 25-(OH)D levels at birth were independent risk factors for the development of BPD. At the same time, At the same time, the long-term lung function damage of children in the BPD group was significantly more than that in the non-BPD group, , which also suggests that the serum 25-(OH)D level at birth and the occurrence of BPD in preterm infants have a suggestive role in long-term lung function impairment. Therefore, in order to prevent the occurrence of neonatal BPD and long-term lung function damage, regular pregnancy checkups can be taken for pregnant women to prevent premature delivery. Active treatment of infections and inflammatory diseases in pregnant women can avoid causing mother and infant inflammatory reactions. Timely supplementation of vitamin D intake can promote fetal lung maturity and other measures.

In conclusion, the present study suggests that serum 25-(OH)D levels at birth in preterm infants may be involved in regulating the occurrence and development of BPD and can affect the long-term pulmonary function situation in the affected infants. This study provides a theoretical basis for the early prevention and individualized treatment of BPD and long-term lung function impairment in preterm infants.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/tp-21-494

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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. All procedures

performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Haikou Maternal and Child Health Hospital (No. 2017062) and informed consent was obtained from infants' parents.

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