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Role of Maternal Micronutrient Status in the Formation of Respiratory Adaptation in Newborns: A Pathogenetic and Clinical Analysis

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Abstract This review summarizes current evidence on the role of micronutrient status and oxidative stress in the development of impaired respiratory adaptation processes in preterm neonates. It has been demonstrated that in respiratory distress syndrome (RDS), oxidative damage to lipids, proteins, and DNA is intensified, as indicated by increased levels of malondialdehyde (MDA, a marker of lipid peroxidation), advanced oxidation protein products (AOPPs), and 8-hydroxy-2-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage. At the same time, total antioxidant capacity (TAC) decreases, reflecting insufficient antioxidant defense in the early neonatal period and potentially accompanied by reduced levels of trace elements acting as cofactors of antioxidant systems. The aim of this review was to analyze the relationship between vitamin D, zinc, and selenium status, as well as markers of oxidative damage and antioxidant defense, and the risk of respiratory distress syndrome, bronchopulmonary dysplasia, duration of mechanical ventilation, mortality, and infectious complications. The material included clinical studies and analytical publications evaluating levels of 25-hydroxyvitamin D [25(OH)D], trace elements, markers of oxidative damage, and clinical outcomes, with emphasis on quantitative measures of association. The analysis demonstrated that in very-low-birth-weight (VLBW) infants, deficiency of 25(OH)D (<20 ng/ml) is associated with an increased risk of respiratory distress syndrome (OR 4.32; $p = 0.010$) and bronchopulmonary dysplasia (OR 4.11; $p = 0.035$). Biomarkers such as AOPPs and 8-OHdG were associated with disease severity, duration of ventilation, and adverse outcomes. Data from interventional studies indicate that selenium supplementation in preterm infants is associated with a reduced incidence of late-onset neonatal sepsis. In conclusion, micronutrient status and indicators of oxidative damage represent a potentially modifiable component of risk; future studies require standardization of deficiency thresholds and respiratory outcome definitions.

Keywords Preterm neonates, Extremely low birth weight, Respiratory distress syndrome, Bronchopulmonary dysplasia, Oxidative stress, 25-hydroxyvitamin D, Zinc

1. Introduction

Respiratory distress syndrome (RDS) in preterm neonates is associated with an imbalance between the production of reactive oxygen species and the capacity of antioxidant defense systems. After birth, the infant transitions from the intrauterine environment to conditions with a higher oxygen concentration, which is accompanied by increased oxidative reactions. Clinical studies have shown that neonates with RDS, compared with control groups, exhibit higher levels of biomarkers of oxidative damage to lipids, proteins, and DNA (MDA, AOPPs, and 8-OHdG) and lower total antioxidant capacity (TAC). At the same time, decreased serum concentrations of zinc and copper—trace elements required for the function of antioxidant enzymatic systems—have been reported. This further aggravates the imbalance between oxidation and antioxidant protection and increases the vulnerability of lung tissue [1–3].

The clinical relevance of these indicators is determined by their association with the severity of RDS. Higher levels of AOPPs and 8-OHdG have been associated with more pronounced impairment of gas exchange and a longer need for respiratory support, including mechanical ventilation. They have also been linked to a higher risk of adverse outcomes. These findings suggest that markers of oxidative damage and antioxidant defense may serve as objective parameters for assessing disease severity and prognosis in preterm neonates with RDS [4].

Vitamin D is considered a nutritional factor involved in the regulation of inflammatory responses and reparative processes in the lungs. In preterm infants with very low birth

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weight (VLBW, <1500 g), deficiency of 25-hydroxyvitamin D [25(OH)D] at birth (<20 ng/ml) has been associated with a higher probability of respiratory distress syndrome (OR 4.32; p = 0.010) and bronchopulmonary dysplasia (OR 4.11; p = 0.035). These findings support the inclusion of 25(OH)D assessment in the perinatal micronutrient profile as a potentially modifiable risk factor for impaired respiratory adaptation [5].

Aim and objectives of the study

The aim of this review was to evaluate the association between the levels of vitamin D, zinc, and selenium, as well as indicators of oxidative damage and antioxidant defense, with respiratory adaptation and outcomes of respiratory distress syndrome in preterm neonates (VLBW <1500 g; ELBW <1000 g).

2. Materials and Methods

The review was conducted according to the PICO framework (Population—Exposure—Comparison—Outcomes). The population included preterm neonates, including infants with very low birth weight (<1500 g) and extremely low birth weight (<1000 g). The analyzed outcomes included respiratory distress syndrome, bronchopulmonary dysplasia, duration of mechanical ventilation, mortality, infections, and markers of oxidative damage and antioxidant defense.

The literature search was performed using the electronic scientific database PubMed for publications from 2015 to 2026. The summary incorporated quantitative indicators reported in the original studies, including odds ratios, relative risks, mean differences, and standardized mean differences [2,6–8].

3. Results and Discussion

In preterm neonates with respiratory distress syndrome (RDS), compared with the control group, consistent changes in indicators of oxidative damage and antioxidant defense are observed. Clinical data demonstrate increased markers of lipid peroxidation, protein oxidation, and DNA damage (MDA, AOPPs, and 8-OHdG), accompanied by a simultaneous decrease in total antioxidant capacity (TAC). Against this background, a reduction in trace elements involved in the functioning of antioxidant enzyme systems—primarily zinc and copper—is also recorded. This finding confirms the development of a pronounced imbalance between enhanced oxidative processes and weakened protective mechanisms in infants with RDS [1,4].

The prognostic value of oxidative stress markers is determined by their association with clinical severity and the need for respiratory support. Higher levels of AOPPs and 8-OHdG are associated with more severe impairment of oxygenation and with longer durations of mechanical ventilation and hospitalization. Several indicators demonstrate statistically significant correlations with severity indices. Research data also present threshold values obtained using ROC analysis, as well as predictive accuracy parameters (AUC, sensitivity, and specificity) for identifying severe disease and the risk of adverse outcomes, including mortality. These findings support the potential clinical application of these markers for risk stratification [1,9].

From a clinical perspective, these results confirm that the degree of oxidative damage reflects not only the presence of RDS but also the severity of its course. In practical terms, this means that the combination of elevated levels of MDA, AOPPs, and 8-OHdG with reduced total antioxidant capacity and deficiency of zinc and copper forms an unfavorable biochemical profile associated with a prolonged need for intensive care. This profile is consistent with the pathogenesis of RDS, in which hyperoxic exposure, inflammatory responses, and damage to the surfactant system are amplified under conditions of limited antioxidant protection [4,7].

A separate body of evidence concerns vitamin D in preterm infants with very low birth weight (VLBW, <1500 g). In a study evaluating 25-hydroxyvitamin D [25(OH)D] levels at birth, deficiency (<20 ng/ml) was associated with an increased risk of respiratory distress syndrome (odds ratio [OR] 4.32; p = 0.010) and bronchopulmonary dysplasia (OR 4.11; p = 0.035). These quantitative findings indicate that vitamin D insufficiency in the early neonatal period is associated with adverse respiratory outcomes and may be considered a clinically significant nutritional risk factor in VLBW infants [10].

In preterm neonates with very low birth weight (VLBW, <1500 g), vitamin D deficiency at birth is regarded as a clinically significant determinant of unfavorable respiratory outcomes. It has been shown that a 25(OH)D level <20 ng/ml is associated with an increased probability of respiratory distress syndrome (OR 4.32; p = 0.010) and bronchopulmonary dysplasia (OR 4.11; p = 0.035). These findings demonstrate a statistically significant relationship between vitamin D deficiency and the development of both early and later respiratory dysfunctions in high-risk neonates [5,11].

Additional findings confirm the prognostic value of measuring 25(OH)D in umbilical cord blood in preterm infants, including VLBW infants and those with extremely low birth weight (ELBW, <1000 g). Vitamin D deficiency was more frequently detected in infants who subsequently developed bronchopulmonary dysplasia. In multivariate models, 25(OH)D levels remained independently associated with the risk of this complication, while determination of threshold values using ROC analysis and reporting of the area under the curve (AUC) allowed this parameter to be considered a potential biomarker for early prediction of bronchopulmonary dysplasia [12].

From a methodological perspective, uniformity in measurement techniques and clinical definitions is of fundamental importance. In the study under consideration, 25(OH)D levels were determined using laboratory methods in umbilical cord blood samples. Deficiency was classified according to established threshold values, and respiratory outcomes were recorded based on clinical diagnostic criteria

for respiratory distress syndrome and bronchopulmonary dysplasia. Such an approach ensures comparability of data between study groups and allows their application in clinical practice, provided that laboratory methods and diagnostic criteria are standardized [6,7,12].

In preterm neonates with very low birth weight (VLBW, <1500 g), deficiency of 25(OH)D at birth (<20 ng/ml) is associated with an increased risk of adverse respiratory outcomes. It has been shown that at concentrations <20 ng/ml the probability of respiratory distress syndrome increases (OR 4.32; p = 0.010), and the risk of bronchopulmonary dysplasia also rises (OR 4.11; p = 0.035). These findings confirm the clinical significance of assessing 25(OH)D levels in the early neonatal period for risk stratification in the VLBW population [7,10].

An additional clinically important approach is the measurement of 25(OH)D in umbilical cord blood as an early prognostic marker of bronchopulmonary dysplasia in preterm infants, including those with extremely low birth weight (ELBW, <1000 g). In studies analyzing cord blood samples, vitamin D deficiency was widely prevalent and was more frequently detected in infants who subsequently developed bronchopulmonary dysplasia. The authors presented a multivariate logistic regression model and identified threshold values for 25(OH)D based on ROC analysis with reporting of the area under the curve, allowing the cord blood level of 25(OH)D to be considered a potential indicator for early prediction of bronchopulmonary dysplasia [7,12].

For correct interpretation of the results, comparable measurement methods and unified criteria for defining deficiency and clinical outcomes are essential. In the present study, 25(OH)D levels were determined by laboratory analysis of umbilical cord blood samples; deficiency was classified according to established thresholds, while respiratory outcomes —respiratory distress syndrome and bronchopulmonary dysplasia—were diagnosed based on clinical criteria. This approach ensures reproducibility of comparisons between groups and enhances the clinical applicability of the findings when methods are described in a standardized manner [10,12].

4. Conclusions

In preterm neonates, respiratory distress syndrome is accompanied by a pronounced increase in oxidative damage, reflected by elevated levels of MDA, AOPPs, and 8-OHdG, together with a decrease in total antioxidant capacity (TAC), indicating insufficient antioxidant defense in the early neonatal period. Elevated levels of AOPPs and 8-OHdG are associated with greater severity of respiratory distress syndrome, longer duration of mechanical ventilation, and an increased risk of adverse outcomes, including mortality.

Vitamin D deficiency at birth [25(OH)D <20 ng/ml] is associated with an increased risk of respiratory distress syndrome (odds ratio 4.32; p = 0.010) and bronchopulmonary dysplasia (odds ratio 4.11; p = 0.035). Measurement of 25(OH)D in umbilical cord blood may be used as an early biomarker for predicting the risk of bronchopulmonary dysplasia when threshold values are determined using ROC analysis.

Enteral selenium supplementation in neonates with very low birth weight has been associated with a reduced incidence of late-onset neonatal sepsis, highlighting the clinical importance of correcting micronutrient deficiencies in high-risk populations.

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