European Journal of Biomedical and Life Sciences

№ 1–2 2021

PREMIER
Publishing

Vienna
2021

https://doi.org/10.29013/ELBLS-21-1.2-20-23

Lezhenko Hennadii Olexandrovych
Zaporizhzhia State Medical University
MD, PhD, DSc, Head of the Hospital Pediatrics Department
E-mail: genalezh@gmail.com
Pogribna Anastasiia Olexandrivna,
Zaporizhzhia State Medical University
PhD-Student, Hospital Pediatrics Department
Zaporozhye, Ukraine
E-mail: a.pogrebnaia@gmail.com

INFLUENCE OF VITAMIN D STATUS ON THE SEVERITY OF ANEMIA OF INFLAMMATION IN YOUNG CHILDREN WITH ACUTE INFLAMMATORY BACTERIAL RESPIRATORY DISEASES

Abstract. We have studied the effect of vitamin D status on the severity of anemia of inflammation in young children with acute inflammatory bacterial respiratory diseases. Some indicators of iron metabolism were analyzed depending on the level of vitamin D in the blood serum in the understanding the development of anemia of inflammation.

Keywords: anemia of inflammation, vitamin D, erythropoietin, ferritin, young children.

Due to the expansion of researches on the extraskeletal functions of vitamin D, its potential role in iron homeostasis and erythropoiesis has been described. An increase in pro-inflammatory cytokines suppresses erythropoiesis in the bone marrow and shortens the life span of erythrocytes due to increased activation of macrophages and erythrophagocytosis in anemia of inflammation (AI). A decrease in proinflammatory cytokines and, as a consequence, hepcidin caused by the influence of vitamin D can increase the bioavailability of iron for erythropoiesis and hemoglobin synthesis by restoring iron recirculation, preventing iron sequestration in macrophages, eliminating disorders of iron absorption, thereby preventing the development of AI. On the other side, inflammatory cytokines can disrupt erythropoiesis by suppressing the production of erythropoietin (EPO), as well as the differentiation and proliferation of erythroid progenitor cells [1, 1011–1023]. However, vitamin D supports erythropoiesis by increasing the proliferation of erythroid precursors and a synergistic effect with EPO [2, 403–409; 3, 121–127; 4, 432–438; 5, 1672–1679]. Previous studies suggest that an additional pleiotropic benefit of vitamin D supplementation may be to reduce the severity of anemia and increase sensitivity to EPO [6, 447–452].

Aim. To determine the relationship between the level of vitamin D in the blood serum and the severity of AI in young children with acute inflammatory bacterial diseases of the respiratory system.

Materials and methods. A total of 40 children aged between 1 month and 3 years (with an average age of 1,6 ± 0.4 years) were examined. The main group consisted of 20 children with acute bacterial diseases of the respiratory tract. In the main group, bronchitis was diagnosed in 14(70%) children, pneumonia – in 6(30%) children. Given the hematological picture, the main group was divided into two subgroups. The first subgroup included

10 children with AI, which was determined 4–5 days after the disease onset. The second subgroup consisted of 10 children without anemia. The comparison group was represented by 10 children with iron deficiency anemia (IDA) without inflammatory manifestations. The control group included 10 conditionally healthy children. The studied groups were representative in age and sex of the children. All study patients on a planned basis received a vitamin D3 supplement according to clinical guidelines.

The content of vitamin D in the blood serum of children of the observation group was determined. It was established that the level of 25(OH)D_3 ≤ 30 ng/ml was observed in the first subgroup in 4(40%) children, in the second subgroup – in 5(50%) children, in the comparison group – in 3(30%) children. In the control group, there was no evidence of vitamin D deficiency. The level of 25(OH)D_3 30–45 ng/ml was found in the first subgroup in 5(50%) children, in the second subgroup in 4(40%) children, in the comparison group – in 6(60%) children, in the control group – in 6(60%) children. The level of 25(OH)D_3 ≥ 45 ng/ml was detected in the first, second subgroup, as well as in the comparison group in 1(10%) child, in the control group – in 4(40%) children.

Blood serum 25(OH)D_3, erythropoietin, and ferritin levels were measured by enzyme-linked immunosorbent assay (ELISA) using commercial kits: 25OH Vitamin D Total ELISA (DIAsourceImmunoAssays S.A., Belgium), EPO (Erythropoietin) ELISA (Biomerica, Germany), Ferritin ELISA (ORGENTEC DiagnostikaGmbH, Germany).

Statistical analysis of the data was performed using the statistical packages «EXCEL» and "Statistica 13.0" (StatSoft Inc. No. JPZ8041382130ARCN10-J). Normality of the data was checked using the Shapiro-Wilk test. We used the method of correlation analysis with the Spearman correlation coefficient calculation**.** Measurement data of a non-normal distribution and non-linear dependence were expressed as a median and quartile (Me (Q25; Q75)). To assess the differences in indicators, the nonparametric Mann-Whitney U-test was calculated as a nonparametric analogue of the Student criterion. Differences were considered at a significance level of $p < 0,05$.

All procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional and National Research Committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. An informed consent was obtained from all individual participants included in the study. The full data set of children, their parents, and physician that support the findings of this study were not publicly available due to the restrictions of the ethics approval originally obtained.

Results. In this study, we determined the change in markers of iron metabolism in the observation groups depending on the level of vitamin D in the blood serum. We have previously described the hematological picture in study patients [7, 473–478].

At a level of 25(OH)D_3≤30 ng/ml in the first subgroup moderate and mild anemia was observed with a hemoglobin content of 95(87; 106) g/L. With an increase in the content of 25(OH)D_3 in the blood serum of children with AI there was a tendency to an increase in the hemoglobin level, and the anemia was characterized by a mild severity: at a 25(OH)D_3 level of 30–45 ng/ml hemoglobin was 106(100; 109) g/L. Only in 1 patient from the first subgroup the 25(OH)D_3 content exceeded 45 ng/ml, while the hemoglobin index was 107 g/L, which is 1,3 times ($p<0,05$) higher than the indicators of the first quartile of the hemoglobin level detected at 25(OH)D_3 level ≤30 ng/ml. A similar clinical picture was observed in the comparison group: with vitamin D deficiency, the hemoglobin level was 96,5 (95; 106) g/l, with 25(OH)D_3 30–45 ng/ml – 107 (96,5; 109) g/L, and only in one case 25(OH)D_3≥45 ng/ml, while the hemoglobin content was limited to 106 g/L. In the second subgroup, a tendency towards an increase in the hemoglobin level was also revealed, proportional to the increase in the 25(OH)D_3 content. At a level of 25(OH)D_3 ≥45 ng/ml, the hemoglobin content

reached 136 g/L, while with a level of vitamin D provision in the range of 30–45 ng/ml, the hemoglobin index was 119 (110; 129,5) g/L, at $25(OH)D_3 \leq$ ≤ 30 ng/ml – 113 (110; 129) g/L. In the control group there was no deficiency in the provision of vitamin D.

The data on the EPO level in the blood serum of the studied patients are quite indicative. Thus, in the first subgroup, the EPO level at $25(OH)D_3 \geq 45$ ng/ml was 1,8 times higher than its content at $25(OH)D_3 \leq 30$ ng/ml and 1,5 times higher at $25(OH)D_3$ 30–45 ng/ml (6,8 ng/ml versus 3,85 (3,5; 5,75) ng/ml and 4,5 (4,2; 4,5) ng/ml, respectively, $p<0.05$). 1,5 times the EPO content at $25(OH)D_3 \geq 45$ ng/ml its level at $25(OH)D_3 \leq 30$–45 ng/ml in the second subgroup (6,53 ng/ml, 4,35 (3,3; 4,5) ng/ml and 4,5 (4,35; 5,75) ng/ml, respectively, $p<0.05$) and the comparison group (27,0 ng/ml, 23,5(20,5; 29,5)ng/ml and 18,0 (14,0; 20,5) ng/ml, $p<0.05$).

In the first subgroup the ferritin content at $25(OH)D_3 \leq 30$ ng/ml was 1,3 times higher than its content in the groups of children with a sufficient level of vitamin D provision (63,0(48,0; 78,0) ng/ml, 47,75 (38,0; 55,0) ng/ml, 48 ng/ml, respectively, $p <0,05$). The tendency to its increase at $25(OH)D_3 \leq 30$ ng/ml was also observed in the second group (52,0 (45,0; 68,0) ng/ml, 47,7 (34,0; 50,2) ng/ml and 45 ng/ml, $p>0,05$). In the comparison group the ferritin level at $25(OH)D_3 \leq 30$ ng/ml was 2 times higher than its values at the content of vitamin $25(OH)D_3 \geq 45$ ng/ml (48,0 (43,5; 50,0) ng/ml, 23 ng/ml, $p<0.05$), and at $25(OH)D_3 \leq$ ≤ 30–45 ng/ml, there was a tendency to its decrease (39,8 (33,0; 47,5) ng/ml, $p<0.05$).

We revealed a weakening of correlations with an insufficient level of vitamin D. Thus, at $25(OH)D_3 \leq 30$ ng/ml, a weak inverse correlation was noted between it and ferritin ($r= –0,12$, $p<0,05$), and a moderate straight correlation – with hemoglobin ($r =0,31$, $p <0,05$) and EPO ($r =0,3$, $p <0,05$). At the same time, at $25(OH)D_3 >30$ ng/ml, a moderate inverse correlation was observed between it and ferritin ($r= –0,36$, $p<0,05$), and a moderate straight correlation – with hemoglobin ($r=0,6$, $p<0,05$) and EPO ($r=0,5$, $p<0,05$).

Discussion. In the course of this study, we examined the potential relationship between vitamin D status and the corresponding dynamics of some indicators of iron metabolism. We noted a statistically significant decrease in hemoglobin concentration proportional to an increase in vitamin D deficiency. This suggests that vitamin D deficiency may be a potential risk factor for the development of AI. In support of our hypothesis there is evidence from studies that described an investigative relationship between $25(OH)D_3$ and $1,25(OH)_2D_3$ deficiency and the prevalence of anemia [8, 715–720; 9, 564–572]. Determination of a positive correlation relationship between the concentrations of hemoglobin and erythropoietin with vitamin D in the blood serum probably indicates a protective role of vitamin D against erythropoietic disorders. Icardi A. et al. (2013) described the inverse relationship between $25(OH)D_3$ status and EPO [8, 715–720], which can be explained by the involvement of the reticuloendothelial system in the implementation of the immune defense reaction, due to which the synthesis of hepcidin increases with a decrease in the availability of iron, which will naturally lead to resistance to EPO and the development of anemia [5, 1672–1679]. The dynamics of ferritin value depending on the vitamin D status suggests that the need for iron sequestration as a protective reaction is inversely proportional to the protective function carried out by vitamin D, which may indicate ineffective erythropoiesis in patients with insufficient $25(OH)D_3$ provision. Another possible mechanism is that vitamin D directly stimulates erythroid precursors. Thus, it was studied that an increase in the concentration of $25(OH)D_3$ reduces the expression of ferritin mRNA, and immunohistochemical analysis of the ferritin protein confirmed that the effect of $25(OH)D_3$ also leads to a decrease in the expression of the protein itself [9, 564–572; 10, 1650–1658]. Based on the data presented in this study, we hypothesize that vitamin D metabolites are likely to maintain the expression of ferroportin in

the membrane, and its loss is associated with intracellular iron deposition through ferritin, which, in turn, leads to AI of the iron-redistribution genesis. This is of direct importance for the control of systemic homeostasis. In this situation, the functioning of vitamin D, aimed at protecting adequate erythropoiesis, is consistent with its intracellular antibacterial activity. The mechanisms described above support our hypothesis that low vitamin D status may be a contributing factor to AI. At the same time, the active form of vitamin D can affect erythropoiesis by stimulating the proliferation and maturation of erythroid progenitor cells, and this may explain the positive effect of vitamin D in reducing the severity of AI.

Thus, according to the results of the study, it can be argued that the severity of the course of anemia of inflammation is determined by the level of vitamin D deficiency, which is apparently due to its effect on erythropoiesis due to sensitivity to EPO and possible indirect effects on ferritin synthesis.

References

1. Guenter Weiss, Lawrence T. Goodnough. N Engl J Med: Anemia of chronic disease,– Vol. 352.– Issue 10, 2005. Doi: 10.1056/NEJMra041809.
2. Dora Ben Alon, Cidio Chaimovitz, Alexander Dvilansky, Gilles Lugassy, Amos Douvdevani, Shraga Shany, Ilana Nathan. Exp Hematol: Novel role of 1,25(OH)(2) D(3) in induction of erythroid progenitor cell proliferation,– Vol. 30.– Issue 5. Doi: 10.1016/s0301–472x(02)00789–0.
3. Filippo Aucella, Rosario Potito Scalzulli, Giuseppe Gatta, Mimmo Vigilante, Angelo Michele Carella, Carmine Stallone. Nephron Clin Pract: Calcitriol increases burst-forming unit-erythroid proliferation in chronic renal failure. A synergistic effect with r-HuEpo,– Vol. 95.– Issue 4. 2003. Doi: 10.1159/000074837.
4. Ellen M. Smith Vin Tangpricha. Curr Opin Endocrinol Diabetes Obes: Vitamin D and anemia: insights into an emerging association,– Vol. 22.– Issue 6. 2015. Doi: 10.1097/MED.0000000000000199.
5. Andrea Icardi, Ernesto Paoletti, Luca De Nicola, Sandro Mazzaferro, Roberto Russo, Mario Cozzolino. Nephrol Dial Transplant: Renal anaemia and EPO hyporesponsiveness associated with vitamin D deficiency: the potential role of inflammation,– Vol. 28.– Issue 7. 2013. Doi: 10.1093/ndt/gft021.
6. John J. Sim Peter T. Lac, In Lu A. Liu Samuel O. Meguerditchian, Victoria A. Kumar, Dean A. Kujubu, Scott A. Rasgon. Ann Hematol: Vitamin D deficiency and anemia: a cross-sectional study,– Vol. 89.– Issue 5. 2010. Doi: 10.1007/s00277–009–0850–3.
7. Hennadii Lezhenko, Anastasiia Pogribna. Zaporozhye medical journal: The role of hepcidin in the pathogenetic mechanisms of anemia of inflammation development in young children with acute inflammatory bacterial diseases of the respiratory system,– Vol. 22.– Issue 4. 2020. Doi: 10.14739/2310–1210.2020.4.208356.
8. Neha M. Patel Orlando M. Gutiérrez, Dennis L. Andress, Daniel W. Coyne, Adeera Levin, Myles Wolf. Kidney Int: Vitamin D deficiency and anemia in early chronic kidney disease,– Vol. 77.– Issue 8. 2010. Doi: 10.1038/ki.2009.551.
9. Justine Bacchetta, Joshua J. Zaritsky, Jessica L. Sea, Rene F. Chun, Thomas S. Lisse, Kathryn Zavala, Anjali Nayak, Katherine Wesseling-Perry, Mark Westerman, Bruce W. Hollis, Isidro B. Salusky and Martin Hewison. JASN: Suppression of Iron-Regulatory Hepcidin by Vitamin D,– Vol. 25.– Issue 3. 2014. URL: https://doi.org/10.1681/ASN.2013040355.
10. Sana Syed, Ellen S. Michalski, Vin Tangpricha, Supavit Chesdachai, Archana Kumar, Jarod Prince, Thomas R. Ziegler, Parminder S. Suchdev, Subra Kugathasan. Inflammatory Bowel Diseases: Vitamin D Status Is Associated with Hepcidin and Hemoglobin Concentrations in Children with Inflammatory Bowel Disease,– Vol. 23.– Issue 9. 2017. Doi.org/10.1097/MIB.0000000000001178.

Contents