Prevalence and correlates of vitamin K deficiency in children with inflammatory bowel disease

Jan K. Nowak1, Urszula Grzybowska-Chlebowczyk2, Piotr Landowski3, Anna Szafarska-Paplawska4, Beata Klincewicz1, Daria Adamczak5, Tomasz Banasiewicz6, Andrzej Pławska7 & Jarosław Walkowiak1

1Poznan University of Medical Sciences, Department of Pediatric Gastroenterology and Metabolic Diseases, Poznan, Poland, 2Medical University of Silesia, Department of Paediatrics, Katowice, Poland, 3Medical University of Gdansk, Department of Pediatrics, Pediatric Gastroenterology, Hepatology and Nutrition, Gdansk, Poland, 4Nicolaus Copernicus University, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Department of Pediatric Endoscopy and Gastrointestinal Function Testing, Bydgoszcz, Poland, 5Poznan University of Medical Sciences, Poznan, Poland, 6Poznan University of Medical Sciences, Department of General, Gastroenterological and Endocrinological Surgery, Poznan, Poland, 7Institute of Human Genetics, Polish Academy of Sciences, Poznan, Poland.

Although vitamin K deficiency has been implicated in adult inflammatory bowel disease (IBD), its prevalence in pediatric IBD remains unknown. We carried out a cross-sectional study in 63 children with Crohn’s disease (CD) and 48 with ulcerative colitis (UC) to assess the prevalence of vitamin K deficiency and to search for potential correlation between vitamin K status and pediatric IBD activity. Vitamin K status was assessed using protein induced by vitamin K absence-II (PIVKA-II; ELISA). Prevalence of vitamin K deficiency was 54.0% in CD and 43.7% in UC. Vitamin K deficiency was more common in patients with higher CD activity, in CD patients with higher mass Z-scores, and less common among children with CD treated with infliximab. Relation of vitamin K deficiency to pediatric IBD clinical course and treatment demand further research.

Vitamin K is as a group of molecules serving as cofactors of protein carboxylation that leads to creation of gamma-carboxyglutamic acid residues which enable calcium bonding. Several vitamin K-dependent proteins are known. They are involved in coagulation, preservation of bone mineral density and protection against vascular calcification. It is also postulated that vitamin K plays an important role in the central nervous system. Thus, vitamin K deficiency has a range of consequences, of which loss of bone mineral density is the most prominent, as it manifests even before blood coagulation factors production becomes altered.

One of two main substrates of vitamin K-dependent carboxylation used for vitamin K status assessment is protein induced by vitamin K absence-II (PIVKA-II), the other being osteocalcin. Plasma PIVKA-II concentrations were shown to inversely correlate with plasma phylloquinone concentrations. PIVKA-II levels assessment and direct vitamin K concentrations measurements have shown that vitamin K deficiency is prevalent in patient populations as different as newborn infants, children with chronic liver disease, hemodialyzed patients, cystic fibrosis patients, the institutionalized elderly, and is also a consequence of treatment with vitamin K antagonists. Vitamin K deficiency has also been reported in chronic gastrointestinal disorders, including inflammatory bowel diseases (IBD). However, to authors’ best knowledge, vitamin K status has not been investigated in children with IBD so far.

The aim of this study was to assess the prevalence of vitamin K deficiency and its correlates in children with Crohn’s disease (CD) and ulcerative colitis (UC).

**Results**

The median PIVKA-II serum concentration [interquartile range] in IBD equaled 2 ng/mL [1.3–3.1]; it was 2.3 [1.3–3.5] in Crohn’s disease, and 1.9 [1.3–2.7] in ulcerative colitis. PIVKA-II levels were equal to or higher than 2 ng/mL in 34 of 63 patients (54.0%) with CD and 21 of 48 patients (43.7%) with UC. Basic clinical features in CD and UC patients with and without vitamin K deficiency are shown in Tables 1 and 2, respectively. The PCDAI and Truelove-Witts scores in patients with and without vitamin K deficiency are illustrated in Fig. 1.
Table 1 | Basic clinical features in Crohn’s disease patients with and without vitamin K deficiency.

| Variables                        | Vitamin K deficiency | p-value |
|----------------------------------|----------------------|---------|
|                                  | Median [1st-3rd quartiles] or percentage |         |
|                                  | No                   | Yes     |         |
| Number of patients               | 29 (46.0%)           | 34 (54.0%)| 0.19   |
| Age (years)                      | 15.0 [12.0–16.2]     | 16.0 [14.0–17.0] |         |
| **Body mass (Z-score)**          | −1.1 [−1.5–[−0.5]]   | −0.4 [−1.3–[−0.0]] | **0.04** |
| Height (Z-score)                 | −0.4 [−1.0–[0.2]]    | −0.3 [−0.9–[0.3]] | 0.41    |
| Disease duration (months)        | 19.0 [7.0–27.0]      | 15.5 [6.2–33.5] | 0.59    |
| Ileal involvement                | 75.9%                | 84.8%   | 0.57 χ² |
| **Pediatric Crohn’s Disease**    | **15.0 [10.0–25.0]** | **22.5 [10.6–50.0]** | **0.04** |
| **Activity Index score**         | **C-reactive protein serum concentration relative to cutoff value** |         |
|                                  | 1.2 [0.5–3.1]        | 1.5 [0.4–2.7] | 0.71    |
| **Hospitalizations**             | 1.0 [0.5–2.0]        | 1.5 [1.0–2.0] | 0.68    |
| **Exacerbations**                | 1.0 [1.0–2.0]        | 1.0 [0.25–2.0] | 0.84    |
| Corticosteroid treatment         | 34.5%                | 55.9%   | 0.09 χ² |
| **Immunosuppressive treatment**  | 58.6%                | 55.9%   | 0.93 χ² |
| **Infliximab**                   | **34.5%**            | **11.8%** | **0.03 χ²** |

(The reason for vitamin K deficiency in IBD remains unclear. It may be hypothesized that vitamin K deficiency results from undernutrition and/or malabsorption caused by IBD and utilized)

Table 2 | Basic clinical features in ulcerative colitis patients with and without vitamin K deficiency.

| Variables                        | Vitamin K deficiency | p-value |
|----------------------------------|----------------------|---------|
|                                  | Median [1st-3rd quartiles] or percentage |         |
|                                  | No                   | Yes     |         |
| Number of patients               | 27 (56.3%)           | 21 (43.7%)| 0.98   |
| Age (years)                      | 14.0 [12.0–16.0]     | 14.0 [13.0–16.0] |         |
| **Body mass (Z-score)**          | −0.7 [−1.0–[−0.1]]   | −1.3 [−1.4–[−0.2]] | 0.07    |
| **Height (Z-score)**             | −0.7 [−1.1–[0.1]]    | −0.9 [−1.7–[0.6]] | 0.73    |
| **Disease duration (months)**    | 24.0 [11.0–44.0]     | 19.0 [11.0–42.0] | 0.79    |
| **Truelove-Witts score**         | 2.0 [0.5–4.0]        | 4.0 [1.0–6.0] | 0.26    |
| **C-reactive protein concentration relative to cutoff value** | 0.5 [0.1–1.4] | 0.1 [0.1–0.8] | 0.21    |
| **Hospitalizations**             | 0.0 [0.0–1.0]        | 1.0 [0.0–1.0] | 0.25    |
| **Exacerbations**                | 0.0 [0.0–1.0]        | 1.0 [0.0–1.0] | 0.09    |
| Corticosteroid treatment         | 25.9%                | 14.3%   | 0.29 Fishers’ exact test |
| **Immunosuppressive treatment**  | 25.9%                | 38.1%   | 0.37 χ² |
Vitamin K deficiency was less common in patients receiving infliximab. This fact points to a possibility that vitamin K status in CD reflects the intensity of inflammation. Further research is needed to clarify whether biological therapy influences vitamin K status in children with Crohn’s disease. In fact, no studies on the relationship between anti-TNF therapies and vitamin K status have been published so far.

It is interesting that while body mass Z-scores of vitamin K-deficient children with CD were higher compared to those who were vitamin K-sufficient, body mass Z-scores in vitamin K-deficient patients with UC were lower than in those who were vitamin K-sufficient. The reasons for higher Z-scores in vitamin K-deficient patients with CD remain unclear.

The study was limited in several aspects. Firstly, vitamin K status was not analyzed directly. It remains an open question if direct measurement of vitamin K concentration in the blood would be more clinically relevant than the measurement of PIVKA-II concentration. Different vitamin K levels may lead to vitamin K sufficiency in different patients. Thus, the estimation of vitamin K status using PIVKA-II concentrations may present an advantage in that it reflects the intensity of inflammation. Further research is needed to clarify whether biological therapy influences vitamin K status in children with Crohn’s disease. In fact, no studies on the relationship between anti-TNF therapies and vitamin K status have been published so far.

The cross-sectional character of the study did not allow for analysis of PIVKA-II concentrations’ evolution along with disease activity changes. No data on dietary intake of vitamin K were available. If there are seasonal variations of vitamin K status, they could have been a source of bias, as the patients were examined at different time points.

Vitamin K deficiency was highly prevalent in pediatric IBD. In CD patients it correlated with a lack of infliximab treatment, a higher pediatric CD activity, and higher body mass Z-scores. Relation of vitamin K deficiency to pediatric IBD clinical course and treatment demand further research.

Methods
A total of 111 children with inflammatory bowel disease (IBD) were included in the study (67 M, 44 F, age range 6–18). Sixty-three were treated for CD and 48 for UC. Diagnoses were established on the basis of clinical, histological, endoscopic and/or radiographic criteria. The inclusion criteria were: CD or UC diagnosed according to the aforementioned standards, and age of 18 years at most. The exclusion criteria were: liver disease not related to IBD, cancer, anti-vitamin K treatment, pregnancy, and diagnosis of AIDS.

Information on age, body mass and height, disease activity and duration, C-reactive protein (CRP) serum concentration, the number of hospitalizations for IBD, the number of IBD exacerbations, and the treatment in use were gathered using a questionnaire distributed among clinicians participating in the study. Disease activity in CD and UC was described using the Pediatric Crohn’s Disease Activity Index (PCDAI) and Truelove-Witts scores, respectively. Z-scores for body mass and height were calculated using data relating to the local population.

Vitamin K status was assessed using PIVKA-II concentration in patients’ blood sera. PIVKA-II concentrations were determined by enzyme immunoassay (Asserachrom PIVKA-II, Roche Diagnostic, Rotkreuz, Switzerland). It was considered that values ≥ 2 ng/mL (detectable values) indicated vitamin K deficiency.

Statistical analyses were performed in the R environment (version 2.14.1; The R Foundation for Statistical Computing, Vienna, Austria) and using STATISTICA 10 (StatSoft Inc., Tulsa, USA). Wilcoxon rank sum test was used to compare subgroups of CD and CU patients who were vitamin K sufficient and vitamin K deficient. Results obtained from logistic regression analysis, multiple regression analysis, Spearman’s correlation test, Pearson’s chi-squared test and Fisher’s exact test are appropriately labeled. The level of significance was set at p < 0.05.

The study was conducted in accordance with the Declaration of Helsinki. Informed and written consent was obtained from patients’ parents and patients who were at least 16 years old. The study design was approved by Poznan University of Medical Sciences Bioethical Committee, Poznan, Poland (decision no 53/11).

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Figure 1 | The Pediatric Crohn’s Disease Activity Index (A) and Truelove-Witts (B) scores in children with and without vitamin K deficiency. Median values, 1st and 3rd quartiles, as well as the minimum and maximum values are shown. The asterisk denotes statistical significance (p = 0.04).
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Author contributions
J.K.N. performed the statistical analysis, took part in data interpretation and drafted the manuscript. U.G.C., P.L., A.S.P., B.K., and T.B. provided the data and revised the manuscript. T.B., A.P., and D.A. took part in data interpretation and revised the manuscript. J.W. designed the study, coordinated data acquisition, analyzed and interpreted the data, drafted and revised the manuscript. All authors read and approved the final manuscript.

Additional information
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