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Vitamin B6 status and chronic chemotherapy-induced peripheral neuropathy: a prospective cohort study among patients with non-metastatic colorectal cancer receiving oxaliplatin-based chemotherapy

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ABSTRACT

Objective Chronic chemotherapy-induced peripheral neuropathy (CIPN) is a long-lasting side-effect of oxaliplatin. Vitamin B6 might play a role in the pathogenesis of CIPN. Therefore, we investigated associations between plasma vitamin B6 markers and the occurrence and severity of chronic CIPN in patients with non-metastatic colorectal cancer (CRC).

Methods and analysis 242 patients with CRC receiving oxaliplatin-based chemotherapy were included. Blood samples were collected at diagnosis (ie, before chemotherapy), and 6 and 12 months after diagnosis (ie, during and after chemotherapy, respectively). Pyridoxal 5′-phosphate (PLP), pyridoxal (PL) and xanthurenic acid:3-hydroxykynurenine (XA:HK) ratio were measured as vitamin B6 markers using liquid chromatography tandem mass spectrometry. Chronic CIPN was assessed 12 months after diagnosis using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN twenty-item scale questionnaire. Prevalence ratios (PRs) and restricted cubic splines (RCSs) were used to assess associations with chronic CIPN occurrence, and linear regressions were used to assess associations with chronic CIPN severity. Analyses were adjusted for age, sex, smoking, alcohol consumption, diabetes and timing of chemotherapy (neoadjuvant/adjuvant/both).

Results Chronic CIPN was found in 80% (n=194) of patients. Higher PLP levels and XA:HK ratios during chemotherapy were associated with lower occurrence of chronic CIPN ($PR_{perdoubling}$ 0.75, 95% CI 0.62 to 0.91 and P_{RCS}<0.05, respectively) and lower chronic CIPN severity ($\beta_{perdoubling}$ −4.54, 95% CI −7.12 to −1.96 and $\beta_{perdoubling}$ −6.30, 95% CI −9.53 to −3.07, respectively). No associations between PL levels and chronic CIPN were observed.

Conclusion Within this population, merely having PLP levels within the normal range, higher vitamin B6 status during chemotherapy was associated with lower occurrence and severity of chronic CIPN. Future research is warranted to investigate causality and the optimal vitamin B6 status during chemotherapy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Chronic chemotherapy-induced peripheral neuropathy (CIPN) is a severe side-effect of oxaliplatin-based chemotherapy that can persist after treatment completion.

⇒ Vitamin B6 status may play a role in the onset of CIPN.

WHAT THIS STUDY ADDS

⇒ In this prospective cohort study among 242 patients with non-metastatic colorectal cancer receiving oxaliplatin-based chemotherapy, higher vitamin B6 status measured during chemotherapy was associated with lower occurrence and severity of chronic CIPN.

⇒ This is the first study assessing the association between both direct and functional biomarkers of vitamin B6 status, measured before, during and after chemotherapy, and chronic CIPN.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Currently, there is no effective prevention or treatment strategy for chronic CIPN. This study provides a first indication that an adequate vitamin B6 status during chemotherapy may be important to prevent chronic CIPN or alleviate chronic CIPN symptoms.

⇒ Future studies should investigate causality and the optimal vitamin B6 status during chemotherapy to ultimately provide nutritional recommendations during oxaliplatin-based chemotherapy.

INTRODUCTION

Oxaliplatin-based chemotherapy is a common treatment strategy for advanced colorectal cancer (CRC).[1–3] Chemotherapy-induced peripheral neuropathy (CIPN) is a severe side-effect of oxaliplatin and is characterised

by symptoms like numbness, pain, weakness and tingling, which mainly occur in the hands and feet.[4] CIPN affects daily functioning and the quality of life.[5] While acute CIPN develops several hours after infusion of oxaliplatin and may disappear within a few days,[6] chronic CIPN usually arises after multiple chemotherapy doses.[7 8] Symptoms of chronic CIPN frequently persist between cycles and can even continue for months or years after treatment completion.[9] Approximately 55%–80% of patients undergoing oxaliplatin-based treatment report chronic CIPN symptoms ~6–25 months after treatment.[7 8 10] So far, no effective prevention or treatment strategy for chronic CIPN has been identified.[11 12] Therefore, it is important to identify potentially modifiable risk factors associated with the occurrence and severity of chronic CIPN.

A nutrient with a potential role in the onset of CIPN is vitamin B6, also known as pyridoxine.[13] Vitamin B6 is a water-soluble vitamin present in various foods including meat, poultry, fish, bananas, legumes, cereals and nuts.[14] Because vitamin B6 acts as a cofactor for multiple enzymes in both the central and peripheral nervous system, it has been suggested that vitamin B6 may have neuroprotective effects.[15] Some studies suggest that a vitamin B6 deficiency (~<20–30 nmol/L pyridoxal 5′-phosphate (PLP)) might be a risk factor for peripheral nerve damage[16–18] and that supplementation with a B-vitamin complex might alleviate peripheral neuropathy symptoms.[19 20] On the contrary, excessive vitamin B6 levels (~>100–180 nmol/L PLP) can be toxic and cause injury to sensory neurons, and thereby exacerbate peripheral neuropathy symptoms.[16 21–23] In view of these inconclusive results, more studies are needed to elucidate the potential relationship between circulating vitamin B6 levels and chronic CIPN.[24] Here, we investigated whether plasma markers of vitamin B6 status are associated with the occurrence and severity of chronic CIPN in patients with non-metastatic CRC receiving oxaliplatin-based chemotherapy.

MATERIALS AND METHODS

Study design and population

Data from the COLON study (COlorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors that influence colorectal tumour recurrence, survival and quality of life; ClinicalTrials.gov identifier: NCT03191110) were used for the current study.[25] Newly diagnosed patients with CRC were recruited from 11 hospitals in the Netherlands and prospectively followed during and after treatment. Exclusion criteria included non-Dutch speaking patients, or patients with a history of CRC or (partial) bowel resection, chronic inflammatory bowel disease, hereditary CRC syndromes, dementia or other mental conditions that impede completion of the questionnaires.

In total, 2107 patients were included in the COLON study. For the current study, we identified patients with non-metastatic CRC (stage <IV) who received oxaliplatin-based chemotherapy (n=383). Recruitment for the COLON study started in 2010. The CIPN questionnaire was implemented in 2014, and therefore, 121 patients, recruited before 2014, did not have data on chronic CIPN. Other patients without data on chronic CIPN (n=8) and those who did not donate any blood (n=12) were excluded, resulting in a total study population of 242 patients with non-metastatic CRC who received oxaliplatin-based chemotherapy (figure 1).

Data collection

Vitamin B6 status

Non-fasting blood samples were collected in EDTA tubes shortly after diagnosis (reflecting status before chemotherapy), 6 months after diagnosis (reflecting status during chemotherapy), and 12 months after diagnosis (reflecting status ~6 months after completion of chemotherapy). After collection, the blood samples were centrifuged at 1300×g at 4°C for 15 min, and plasma was extracted and stored at −80°C. Measures of vitamin B6 status were evaluated as PLP, the biologically active form of vitamin B6,[26] and pyridoxal (PL), the transport form of vitamin B6.[26] In addition, the ratio between xanthurenic acid (XA) and 3-hydroxykynurenine (HK) was determined as a functional marker of vitamin B6 status. The XA:HK ratio reflects a product-substrate pair of the kynurenine pathway, in which PLP has an important role as cofactor.[26] Higher XA:HK ratios reflect higher intracellular vitamin B6 levels.[26] PLP, PL, XA and HK were measured using liquid chromatography tandem mass spectrometry (LC-MS/MS) at BEVITAL AS (Bergen, Norway; www.bevital.no) as described previously.[27]

Self-reported chronic CIPN

Chronic CIPN was defined as persistent complaints ~6 months after the end of chemotherapy. Data on chronic CIPN were collected using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN twenty-item scale (EORTC QLQ-CIPN20).[28] Patients completed this questionnaire 12 months after diagnosis, which corresponds to ~6 months after the end of chemotherapy. The QLQ-CIPN20 consists of 20 questions and comprises three different scales that evaluate sensory (9 items), motor (8 items) and autonomic symptoms (3 items) related to chronic CIPN.[28] An abbreviated 16-question version of this validated questionnaire was used in the current study, as this version was previously shown to be clinically relevant and reliable for assessing chronic CIPN.[29] Patients' responses were recorded on a 4-point Likert scale ranging from (1) not at all to (4) very much. Total scores (between 16 and 64) were divided by the number of relevant questions, resulting in the mean score. Mean scores were linearly transformed to a 0–100 scale.[29] The occurrence of chronic CIPN (yes/no) was defined using sex-specific and age-specific cut-off values (online supplemental file 1), based on mean scores in the general Dutch population.[30] Furthermore, we evaluated the severity of chronic CIPN symptoms by focusing on the total CIPN score (score on 0–100 scale),

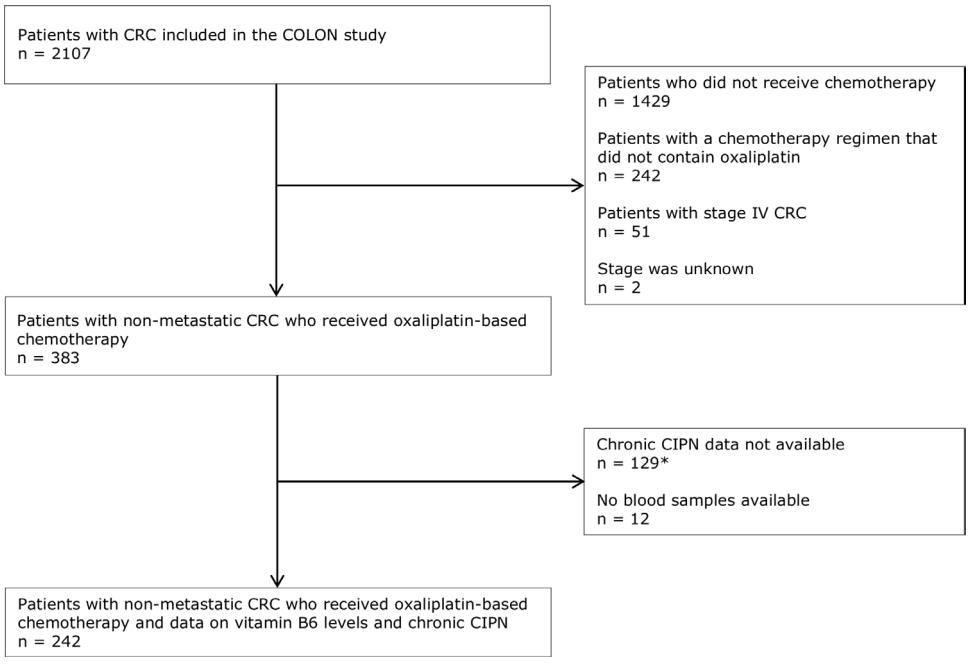

Figure 1 Flowchart representing the patient selection procedure for the current study. *121 patients did not have chronic CIPN data because the questionnaire was not implemented from the beginning of the COLON study. Moreover, another 7 patients had >2 missing items within one subscale of the QLQ-CIPN and 1 patient did not complete the questionnaire at all. CIPN, chemotherapy-induced peripheral neuropathy; CRC, colorectal cancer.

with higher scores reflecting more severe CIPN symptoms.[29] Patients were excluded from the analyses if more than two items of the QLQ-CIPN16 were missing within one subscale (n=8). The remaining missing values of the QLQ-CIPN-16 were handled by the mean-person imputation method, as it was shown that this method resulted in minimum bias in studies using the QLQ-CIPN16 or a comparable questionnaire.[31 32]

Personal, clinical and lifestyle characteristics

Patients completed questionnaires on personal and demographic factors (such as sex, age, body weight and height, smoking and the presence of diabetes) at diagnosis (before chemotherapy), 6 months after diagnosis (during chemotherapy) and 12 months after diagnosis (after chemotherapy). At the same timepoints, a 204-item semiquantitative food frequency questionnaire[33] and a dietary supplement questionnaire, both developed by the Division of Human Nutrition and Health of Wageningen University & Research, the Netherlands, were completed to assess dietary vitamin B6 intake (mg/day), alcohol consumption (g/day) and regular multivitamin use (yes/no), respectively. Regular multivitamin use was defined as intake of a multivitamin supplement at least once per week in the past year (at baseline) or 6 months (during and after chemotherapy). Disease characteristics, such as disease stage, tumour location, treatment regimen and starting oxaliplatin dose were obtained from the Dutch Colorectal Audit[34] and medical files.

Data analyses

The association between markers of vitamin B6 status and the occurrence of chronic CIPN (yes/no) was assessed using Cox proportional hazards regression analyses with a fixed time variable to calculate prevalence ratios (PR) with corresponding 95% CIs. This model was chosen over a logistic regression model, since logistic regression models tend to overestimate risk estimates if the outcome is common.[35] First, restricted cubic splines (RCSs) were created to study the shape of the associations between the markers of vitamin B6 status measured during chemotherapy and chronic CIPN occurrence. Knots were placed at the 10th, 50th and 90th percentiles and the graphs were truncated at the 1st and 99th percentile. Median values of the first tertile of each marker were used as the reference. If associations appeared linear, the PRs were also presented in a continuous manner (per doubling in biomarker). To examine whether markers of vitamin B6 status were associated with chronic CIPN severity (score on 0–100 scale), linear regression analyses were conducted to obtain regression coefficients (β) and 95% CIs. PLP, PL and XA:HK values were log2-transformed to obtain normal distributions. Because of this transformation, risk estimates should be interpreted per doubling in biomarker (level or ratio).

Analyses were adjusted for age and sex.[36–38] Other potential confounders were identified based on available literature, and biological or clinical plausibility. These included body mass index (BMI) (kg/m^2), tumour location (colon or rectum), disease stage (II or III), timing of chemotherapy regimen (neoadjuvant, adjuvant or both), starting dose of oxaliplatin (mg), smoking (current, former or never), alcohol consumption (g/day) and self-reported presence of diabetes (yes/no).[39–42] Potential confounders were added one by one to the models.

If the risk estimates were consistently changed in several models, the potential confounders were included in the final models. Potential confounders were evaluated separately for the analyses on chronic CIPN occurrence and chronic CIPN severity. The final analyses for chronic CIPN occurrence were adjusted for age, sex, smoking, alcohol consumption and the prevalence of diabetes. For chronic CIPN severity, analyses were adjusted for age, sex, smoking, alcohol consumption, the prevalence of diabetes and timing of chemotherapy (neoadjuvant, adjuvant or both). The latter was only added to the model during and after chemotherapy, since the patients did not yet receive chemotherapy at time of diagnosis.

All data analyses were performed using R statistical software (V.4.1.0). The rms package (V.6.6.0) was used to construct the RCSs. Associations were considered statistically significant when 95% CIs did not contain 1 for the Cox regression analyses and did not contain 0 for the linear regression analyses. In the RCSs, p values <0.05 were considered statistically significant.

Patient and public involvement

Participants of the COLON study were involved in defining the research agenda and prioritising topics to be studied in the COLON study. This resulted in the identification of chronic CIPN as one of the outcomes of interest.

RESULTS

In total, 242 patients were included in the current study. The characteristics of the study population at diagnosis are described in table 1. See online supplemental file 2 for the characteristics during and after chemotherapy.

The median [Q1–Q3] age at the time of diagnosis was 63 [59–67] years, and 40% were women. The median [Q1–Q3] BMI was 26.0 [23.9–28.7] kg/m^2. Most patients were diagnosed with stage III cancer (91% vs 9% stage II), and the predominant tumour location was the colon (94% vs 6% rectum). CAPOX (capecitabine combined with oxaliplatin) was the most frequently prescribed chemotherapy regimen (98%). The median vitamin B6 levels were slightly higher before (PLP 40.7 nmol/L, Q1–Q3 27.8–61.3) and after (PLP 43.9 nmol/L, Q1–Q3 31.5–68.1) chemotherapy compared with levels measured during chemotherapy (PLP 33.5 nmol/L, Q1–Q3 24.4–51.7) (p<0.01) (online supplemental file 3). Chronic CIPN was found in 80% (n=194) of the patients 12 months after diagnosis. Among those patients with chronic CIPN, both sensory and motor symptoms were commonly reported (in 82% and 71% of the patients, respectively). The severity of sensory symptoms (median score 25.0) was higher than the severity of motor symptoms (median score 12.5).

Among the patients who experienced chronic CIPN, 38% were women, while among the patients without chronic CIPN, 50% were women. Patients with chronic CIPN had a higher median BMI (26.2 kg/m^2) at diagnosis than patients without chronic CIPN (24.7 kg/m^2). Additionally, patients who experienced chronic CIPN were more often current or former smokers (67%) compared with patients without chronic CIPN (41%).

Vitamin B6 and chronic CIPN occurrence

The association between the XA:HK ratio during chemotherapy and chronic CIPN occurrence appeared to be non-linear. The RCSs showed that, compared with the reference value of 0.19, the occurrence of chronic CIPN decreased with higher XA:HK ratios, and the overall association was statistically significant (P_{RCS}<0.001) (figure 2). Similarly, the association between XA:HK ratio during chemotherapy and motor symptoms related to chronic CIPN was also non-linear and inverse (P_{RCS}<0.001). The other associations were all linear.

Higher PLP levels during chemotherapy were associated with a lower occurrence of chronic CIPN ($PR_{perdoubling}$ 0.75, 95% CI 0.62 to 0.91) (table 2, see online supplemental file 4 for the crude models). The association between PL levels during chemotherapy and chronic CIPN occurrence was not statistically significant ($PR_{perdoubling}$ 0.90, 95% CI 0.75 to 1.07). Higher PLP levels during chemotherapy were associated with a lower occurrence of sensory symptoms and motor symptoms related to chronic CIPN (table 2). Markers of vitamin B6 status measured before and after chemotherapy were not statistically significantly associated with measures of chronic CIPN.

Vitamin B6 and chronic CIPN severity

Higher PLP levels and higher XA:HK ratios during chemotherapy were statistically significantly associated with lower chronic CIPN severity ($\beta_{perdoubling}$ −4.54, 95% CI −7.12 to −1.96 and $\beta_{perdoubling}$ −6.30, 95% CI −9.53 to −3.07, respectively) (table 3, see online supplemental file 5 for the crude models). Both markers of vitamin B6 status were also associated with lower severity of sensory ($\beta_{perdoubling}$ −4.99, 95% CI −8.23 to −1.76 for PLP and $\beta_{perdoubling}$ −7.22, 95% CI −11.28 to −3.17 for XA:HK) and motor symptoms ($\beta_{perdoubling}$ −4.09, 95% CI −6.34 to −1.83 for PLP and $\beta_{perdoubling}$ −5.38, 95% CI −8.22 to −2.54 for XA:HK). No associations between PL levels during chemotherapy and any of the vitamin B6 markers measured before or after chemotherapy and chronic CIPN severity were observed (table 3).

DISCUSSION

In this prospective cohort study, we determined whether circulating markers of vitamin B6 were associated with the occurrence and severity of chronic CIPN in patients receiving oxaliplatin-based chemotherapy for CRC. A higher vitamin B6 status, measured as PLP or XA:HK ratio, during chemotherapy was associated with a reduced occurrence of chronic CIPN and with a lower severity of chronic CIPN symptoms. Vitamin B6 markers measured before or after chemotherapy were not associated with chronic CIPN.

Table 1 Characteristics of the study population

	Total population (n=242, 100%)	Chronic CIPN: yes* (n=194, 80%)	Chronic CIPN: no* (n=48, 20%)
Sex, women	97 (40%)	73 (38%)	24 (50%)
Age at diagnosis, years	63 [59–67]	63 [59–67]	63 [57–69]
BMI at diagnosis, kg/m^2	26.0 [23.9–28.7]	26.2 [24.1–28.7]	24.7 [23.7–28.2]
Tumour stage			
Stage II	21 (9%)	18 (9%)	3 (6%)
Stage III	221 (91%)	176 (91%)	45 (94%)
Tumour location			
Colon	227 (94%)	181 (93%)	46 (96%)
Rectum	15 (6%)	13 (7%)	2 (4%)
Prescribed chemotherapy regimen			
CAPOX	237 (98%)	190 (98%)	47 (98%)
FOLFOX	5 (2%)	4 (2%)	1 (2%)
Smoking at diagnosis			
Current smoker	21 (9%)	18 (9%)	3 (6%)
Former smoker	129 (53%)	112 (58%)	17 (35%)
Never smoker	92 (38%)	64 (33%)	28 (58%)
Alcohol consumption at diagnosis, g/day†	7.9 [1.0–20.4]	7.9 [1.3–21.1]	8.2 [0.6–17.3]
Dietary vitamin B6 intake at diagnosis, mg/day	1.5 [1.2–1.8]	1.5 [1.2–1.8]	1.4 [1.1–1.7]
Regular multivitamin use at diagnosis, yes	49 (20%)	40 (21%)	9 (19%)
Self-reported diabetes at diagnosis, yes‡	26 (11%)	21 (11%)	5 (10%)
Starting dose of oxaliplatin, mg§	250 [240–275]	250 [240–275]	250 [240–255]
Circulating levels at diagnosis¶			
PLP, nmol/L	40.7 [27.8–61.3]	41.1 [28.7–61.3]	40.2 [26.6–61.8]
PL, nmol/L	11.8 [8.3–16.8]	12.3 [8.5–17.2]	11.5 [7.8–15.4]
HK, nmol/L	43.9 [33.2–55.1]	44.0 [34.7–55.9]	43.4 [31.3–53.2]
XA, nmol/L	14.3 [9.9–18.6]	14.6 [10.0–18.9]	14.2 [9.1–18.2]
XA:HK ratio	0.33 [0.24–0.43]	0.33 [0.24–0.43]	0.33 [0.24–0.41]
CIPN score**			
Total peripheral neuropathy score	14.6 [6.3–27.1]	18.8 [10.4–31.3]	0.0 [0.0–2.1]
Sensory subscore	16.7 [8.3–37.5]	25.0 [12.5–37.5]	0.0 [0.0–4.2]
Motor subscore	8.3 [4.2–20.8]	12.5 [8.3–20.8]	0.0 [0.0–1.0]

Data are presented as number (%) or median [Q1–Q3].
*Based on sex-specific and age-specific cut-off values of the total chronic CIPN score, see online supplemental file 1.
†Data missing for eight patients.
‡Based on self-reported information in the questionnaire, missing for five patients.
§Data missing for 12 patients.
¶Data missing for 49 patients.
**Scores on a 0–100 scale.
BMI, body mass index; CAPOX, capecitabine+oxaliplatin; CIPN, chemotherapy-induced peripheral neuropathy; FOLFOX, 5-fluorouracil+leucovorin+oxaliplatin; HK, 3-hydroxykynurenine; PL, pyridoxal; PLP, pyridoxal 5′-phosphate; XA, xanthurenic acid.

In this study, chronic CIPN was found in 80% of the patients with CRC after oxaliplatin-based chemotherapy, which is in line with earlier studies.[7 8 10] While we observed an inverse association between vitamin B6 levels during chemotherapy and chronic CIPN occurrence and severity, previous research has provided contradicting results.[19 20 42 43] In observational analyses of data from a clinical trial among 2450 patients with colon cancer randomly assigned to 6 or 12 cycles of adjuvant FOLFOX with or without 3 years of celecoxib, higher dietary vitamin B6 intake was not associated with CIPN severity during or in the first approximately 6 years after oxaliplatin treatment (OR 1.01, 95% CI 0.84 to 1.21 and OR 1.1, 95% CI 0.92 to 1.31, respectively).[42] It should be noted, however,

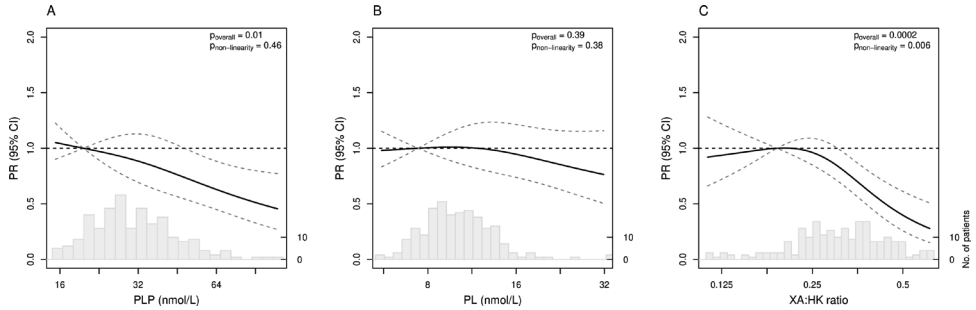

Figure 2 Associations between (A) PLP levels, (B) PL levels and (C) XA:HK ratios measured during chemotherapy and chronic CIPN occurrence in patients with CRC. Biomarker levels and ratios presented as log2 transformed values. Solid lines are restricted cubic splines and dashed lines are 95% CI. The reference values were set at the median level of the first tertile of each marker. Knots were located at the 10th, 50th and 90th percentiles. The X-axis displays the back-transformed values. Analyses were adjusted for age, sex, smoking, alcohol consumption and the prevalence of diabetes. CIPN, chemotherapy-induced peripheral neuropathy; CRC, colorectal cancer; HK, 3-hydroxykynurenine; PL, pyridoxal; PLP, pyridoxal 5′-phosphate; PR, prevalence ratio; XA, xanthurenic acid.

that dietary B6 intake is difficult to capture using common dietary assessment instruments, and dietary vitamin B6 intake is only moderately associated with circulating PLP levels.[44 45] Moreover, in a cross-sectional study among patients who already had neuropathy (including diabetic, HIV and chemotherapy-induced) for an average of 6 years, the association between higher plasma B6 levels (>202 nmol/L PLP or >177 nmol/L pyridoxine) and chronic idiopathic axonal polyneuropathy symptoms was assessed.[43] Higher B6 status compared with normal B6 status (20–202 nmol/L PLP) was not associated with patient-reported neuropathy symptoms (paresthesia OR 1.00, 95% CI 0.98 to 1.01 and numbness OR 1.00, 95% CI 0.995 to 1.002). While the neuropathy symptoms of these patients may not all originate from chemotherapy, the results are comparable to our study where we also did not observe associations for vitamin B6 status measured after chemotherapy. In a randomised placebo-controlled trial, the effect of a B-vitamin complex including vitamin B6 as pyridoxine (60 mg/day) on the incidence of CIPN symptoms 12 weeks post-chemotherapy was assessed among 71 patients diagnosed with various types of cancer receiving either oxaliplatin, taxanes or vincristine chemotherapy.[19] The intervention did not result in a significant reduction of CIPN scores (p>0.05), but patients consuming the B-vitamin complex did perceive reduced sensory symptoms compared with the placebo group (p<0.05). It should be noted, however, that the precise role of vitamin B6 alone

Table 2 Association between markers of vitamin B6 status and the occurrence of chronic CIPN in patients with CRC

		Total neuropathy*		Sensory symptoms*		Motor symptoms*
Circulating plasma levels	**n/cases**	**PR (95% CI)**	**n/cases**	**PR (95% CI)**	**n/cases**	**PR (95% CI)**
PLP (nmol/L)†						
Before chemotherapy	182/144	1.04 (0.86 to 1.25)	182/149	0.99 (0.82 to 1.19)	182/127	0.86 (0.70 to 1.06)
During chemotherapy	213/172	0.75 (0.62 to 0.91)‡	213/178	0.72 (0.60 to 0.87)	213/151	0.71 (0.59 to 0.87)
After chemotherapy	153/129	1.08 (0.90 to 1.30)	153/132	1.00 (0.82 to 1.21)	153/114	0.94 (0.77 to 1.16)
PL (nmol/L)†						
Before chemotherapy	182/144	1.11 (0.94 to 1.32)	182/149	1.07 (0.89 to 1.27)	182/127	1.03 (0.86 to 1.24)
During chemotherapy	213/172	0.90 (0.75 to 1.07)‡	213/178	0.87 (0.73 to 1.04)	213/151	0.87 (0.72 to 1.05)
After chemotherapy	153/129	1.14 (0.97 to 1.34)	153/132	1.06 (0.89 to 1.26)	153/114	1.02 (0.84 to 1.23)
XA:HK ratio†						
Before chemotherapy	182/144	0.97 (0.78 to 1.21)	182/149	0.97 (0.77 to 1.22)	182/127	0.96 (0.76 to 1.21)
During chemotherapy	213/172	NL‡	213/178	0.67 (0.54 to 0.82)	213/151	NL
After chemotherapy	153/129	1.00 (0.72 to 1.39)	153/132	0.99 (0.72 to 1.37)	153/114	0.90 (0.64 to 1.27)

Analyses were performed using a Cox proportional hazards regression model with a fixed time variable and adjusted for age, sex, smoking, alcohol consumption and the prevalence of diabetes.
*Based on age-specific and sex-specific cut-off values, see online supplemental appendix 1.
†Circulating plasma levels were log2 transformed, meaning that the PRs should be interpreted per doubling in biomarker.
‡Restricted cubic splines are created for these models (figure 2), 'NL' indicates a non-linear association.
CIPN, chemotherapy-induced peripheral neuropathy; CRC, colorectal cancer; HK, 3-hydroxykynurenine; PL, pyridoxal; PLP, pyridoxal 5′-phosphate; PR, prevalence ratio; XA, xanthurenic acid.

Table 3 Association between markers of vitamin B6 status and the severity of chronic CIPN in patients with CRC

		Total neuropathy score*		Sensory subscore*		Motor subscore*
Circulating plasma levels	n	β (95% CI)	n	β (95% CI)	n	β (95% CI)
PLP (nmol/L)†						
Before chemotherapy	192	−0.05 (−2.79 to 2.68)	192	0.49 (−3.01 to 3.98)	192	−0.59 (−2.95 to 1.77)
During chemotherapy	213	−4.54 (−7.12 to −1.96)	213	−4.99 (−8.23 to −1.76)	213	−4.09 (−6.34 to −1.83)
After chemotherapy	144	1.26 (−2.01 to 4.52)	144	2.01 (−1.96 to 5.98)	144	0.50 (−2.46 to 3.46)
PL (nmol/L)†						
Before chemotherapy	192	2.01 (−0.60 to 4.61)	192	2.30 (−1.04 to 5.64)	192	1.72 (−0.54 to 3.97)
During chemotherapy	213	−1.16 (−3.71 to 1.39)	213	−1.27 (−4.45 to 1.91)	213	−1.05 (−3.29 to 1.18)
After chemotherapy	144	0.92 (−2.11 to 3.95)	144	1.72 (−1.96 to 5.40)	144	0.12 (−2.62 to 2.87)
XA:HK ratio†						
Before chemotherapy	192	−2.19 (−5.28 to 0.91)	192	−2.49 (−6.46 to 1.48)	192	−1.89 (−4.57 to 0.79)
During chemotherapy	213	−6.30 (−9.53 to −3.07)	213	−7.22 (−11.28 to −3.17)	213	−5.38 (−8.22 to −2.54)
After chemotherapy	144	−0.68 (−5.99 to 4.64)	144	0.28 (−6.19 to 6.76)	144	−1.64 (−6.44 to 3.17)

Analyses were performed using linear regression analyses and adjusted for age, sex, smoking, alcohol consumption, the prevalence of diabetes and timing of chemotherapy (neoadjuvant, adjuvant or both). The latter was only added to the model during and after chemotherapy, since the chemotherapy was not yet received by patients at diagnosis.
*Scores on a 0–100 scale.
†Circulating plasma levels were log2 transformed, meaning that the β should be interpreted per doubling in biomarker level or ratio.
CIPN, chemotherapy-induced peripheral neuropathy; CRC, colorectal cancer; HK, 3-hydroxykynurenine; PL, pyridoxal; PLP, pyridoxal 5′-phosphate; XA, xanthurenic acid.

cannot be determined due to the multicomponent nature of the supplement used in this study.

In 2023, the European Food Safety Authority established an upper daily limit for vitamin B6 intake of 12.5 mg/day,[46] due to concerns that excessive, often supplemental, intake of vitamin B6 could result in neurological complaints.[21] Especially, the vitamin B6 form pyridoxine, often present in supplements, has been associated with decreased cell viability in a neuroblastoma cell line.[22] Individual cases have been reported in which vitamin B6 blood levels (mostly measured as PLP) of 88 nmol/L have been linked to neuropathic complaints, although the majority of cases reported complaints with blood levels >183 nmol/L.[23] In our study, as explicitly demonstrated in the RCS analysis, we did not find any evidence that occurrence or severity of chronic CIPN increased with higher levels of the vitamin B6 markers. However, it is worth to mention that there were only very few patients with elevated vitamin B6 levels in our study population (PLP levels >180 nmol/L: n=6 before chemotherapy, n=5 during chemotherapy and n=6 after chemotherapy). Although we cannot exclude potential detrimental effects of vitamin B6 at higher levels, our findings may imply that sufficient vitamin B6 levels during the administration of chemotherapy might be important in regard to chronic CIPN occurrence and severity.

The precise biological mechanisms underlying CIPN development are not entirely understood.[47] The development of CIPN is multifactorial, but the main suggested aetiological mechanisms include mitochondrial toxicities, oxidative stress, DNA damage, axonal transport disruption and ion channel remodelling.[48] Vitamin B6 is a cofactor for numerous biochemical reactions involved in a diverse range of cellular processes[49] including nerve regeneration and synthesis of several neurotransmitters, for example, serotonin, dopamine and gamma-aminobutyric acid.[15] Deficiencies in these neurotransmitters may result in neuronal overactivity and subsequent neurodegeneration.[21] Overall, vitamin B6 is important in restoring nerve function via several physiological processes,[15] which could explain the observed associations with a lower occurrence and decreased severity of chronic CIPN. We did, however, not observe an association between PL levels, the transport form of vitamin B6[26] and chronic CIPN outcomes, implying that particularly the biologically active PLP[26] may be important for the prevention of nerve damage and regeneration during the actual chemotherapy treatment period.[50]

It should be noted that the PLP levels were slightly lower during chemotherapy compared with the other two timepoints, yet they were still within the normal range of an adequate vitamin B6 status.[51] This finding may imply that vitamin B6 status might be affected by the chemotherapy itself, either directly through the biological mechanisms of oxaliplatin[52] or indirectly through changes in diet or dietary supplement use during chemotherapy treatment.[53 54] Therefore, we cannot exclude the possibility of reverse causation indicating that the associations observed between higher levels of vitamin B6 markers and chronic CIPN occurrence and severity might actually reflect efficacy of the treatment. The causal relationship between vitamin B6 status and chronic CIPN is thus an area for future research. In our analysis, we did not adjust for cumulative oxaliplatin dose, given the ambiguous

relationship with chronic CIPN. A higher cumulative dose of oxaliplatin could be linked to a higher occurrence of chronic CIPN, due to the higher (cumulative) exposure. On the other hand, a lower cumulative dose of oxaliplatin could indicate more treatment modifications as a consequence of acute CIPN. Since acute CIPN is a profound risk factor for chronic CIPN,[9] a lower cumulative oxaliplatin dose might also be related to a higher occurrence of chronic CIPN.

The current study comes with some potential limitations. First, although the EORTC questionnaire has been shown to be reliable and valid,[29] patient-reported questionnaires are prone to overestimate CIPN occurrence.[55] It is, however, not likely that vitamin B6 levels are coherent with a possible overestimation of chronic CIPN symptoms. Moreover, we consider the patient's perspective of utmost importance. Second, pre-existing peripheral neuropathy, due to for example diabetes, is a well-established risk factor of CIPN,[56] but no data on pre-existing neuropathy were available in this study. Nevertheless, self-reported diabetes mellitus occurred in 11% of our population and we adjusted our analyses for this. Third, the blood samples were not collected in fasted conditions, making the vitamin B6 markers susceptible to recent dietary intake.[26] This issue is, however, unlikely to cause overestimation of the observed associations, as the variations tend to be non-differential for patients who did and did not develop chronic CIPN. Fourth, the timing of blood sampling was based on the time since diagnosis, not on chemotherapy schedules. For some patients, the second sample that was planned 6 months after diagnosis (ie, during chemotherapy) was collected shortly after completion of oxaliplatin-based chemotherapy (n=91, median [Q1–Q3]: 40 [20–85] days after last cycle), while others were yet to receive their final cycle of oxaliplatin-based chemotherapy (n=122, median [Q1–Q3]: 24 [45–15] days before last cycle). Future studies are warranted to investigate the role of chemotherapy regimens on circulating vitamin B6 levels by measuring circulating vitamin B6 levels at fixed timepoints during chemotherapy cycles. Lastly, due to the observational design of this study, we cannot fully exclude reverse causation and residual confounding. The strengths of this study include thorough assessment of vitamin B6 status using direct and functional biomarkers over time in a well-defined study population. PLP levels and XA:HK ratios, considered independent markers of vitamin B6 status, showed similar results, which diminishes the risk of incidental findings. Furthermore, we could adjust for a comprehensive set of potential confounders due to the availability of extensive data on clinical and lifestyle factors. To the best of our knowledge, this is the first study assessing the association between plasma markers of vitamin B6 status before, during and after chemotherapy and chronic CIPN.

In conclusion, a higher vitamin B6 status measured during chemotherapy was associated with a lower occurrence of chronic CIPN and lower chronic CIPN severity in our population of patients with non-metastatic CRC undergoing oxaliplatin-based chemotherapy. Although, causality and safe upper limits for vitamin B6 status need to be confirmed, these findings highlight the importance of nutritional status in oncology care and might ultimately provide preventive strategies to protect against this distressing side-effect. Future research is warranted to investigate the optimal vitamin B6 status during chemotherapy in order to provide a solid basis for nutritional recommendations during oxaliplatin-based chemotherapy.

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Data availability statement Data are available upon reasonable request. Since the data consist of identifying cohort information, some access restrictions apply and therefore cannot be made publicly available. Data will be shared with permission from the steering committee of the COLON study. Requests for data can be sent to Dr. Dieuwertje Kok, Division of Human Nutrition and Health, Wageningen University & Research, The Netherlands (e-mail: dieuwertje.kok@wur.nl).

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