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Vitamin B-6 Status Correlates with Disease Activity in Rheumatoid Arthritis Patients During Treatment with TNFα Inhibitors

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ABSTRACT

Background: A frequent observation in inflammatory conditions, including rheumatoid arthritis (RA), is low circulating amounts of pyridoxal 5′-phosphate (PLP), the metabolically active form of vitamin B-6. Recently, a functional marker of vitamin B-6 status, the ratio of 3-hydroxykynurenine (HK): xanthurenic acid (XA) in plasma (HK: XA), was proposed.

Objective: We investigated vitamin B-6 status in patients with RA before and after established treatment with TNFα inhibitors.

Methods: We performed a longitudinal study of RA patients (n = 106, 36% men, median age 54 y) starting first treatment with a TNFα inhibitor (infliximab, etanercept, adalimumab, golimumab, or certolizumab). Clinical assessment (Disease Activity Score for 28 standard joints, DAS28), joint ultrasonography, and blood draw were performed at baseline and after 3 mo treatment. Plasma concentrations of PLP, HK, and XA were measured by liquid chromatography–tandem mass spectrometry. Associations of changes in vitamin B-6 markers with change in DAS28 were assessed by generalized additive models regression and with European League Against Rheumatism (EULAR) response categories by linear regression.

Results: At baseline PLP was inversely correlated with CRP ($\rho = -0.27$, $P = 0.007$), whereas HK: XA correlated with DAS28 ($\rho = 0.46$, $P < 0.001$), CRP ($\rho = 0.36$, $P < 0.001$), and ultrasonography scores ($\rho = 0.29$–0.35, $P \leq 0.003$). After 3 mo treatment, the change (a 33% overall reduction) in DAS28 was related to changes in both PLP (ß = −0.28, $P = 0.01$) and HK: XA (ß = 0.33, $P < 0.001$). Good responders (45%) according to EULAR criteria experienced a 31% increase in PLP ($P = 0.003$) and an 11% decrease in HK: XA ($P = 0.1$), whereas nonresponders (24%) experienced a 25% increase in HK: XA ($P = 0.02$).

Conclusion: Two independent measures of vitamin B-6 status confirm an association with disease activity in RA patients. The association of HK: XA with disease activity may also imply perturbations in kynurenine metabolism in RA. This trial was registered at helseforskning.etikkom.no as 2011/490. *J Nutr* 2019;149:770–775.

Keywords: pyridoxal 5′-phosphate, 3-hydroxykynurenine: xanthurenic acid ratio, functional vitamin B-6 status, rheumatoid arthritis, TNFα inhibitors

Introduction

Altered vitamin B-6 status, measured by low circulating concentrations of the metabolically active form pyridoxal 5′-phosphate (PLP) is well established in rheumatoid arthritis (RA) (1–4), as well as other inflammatory conditions (5–7). In RA patients, circulating PLP has been found to be inversely correlated with C-reactive protein (CRP), erythrocyte sedimentation rate, pain level, morning stiffness, and disability score (1, 3).

Low vitamin B-6 intake has been associated with inflammation, both in rats (8) and patients with cardiovascular disease (5). In RA patients, however, low PLP was not associated with dietary inadequacy (1–4), suggesting that the altered vitamin B-6 status is related to inflammatory processes (3). Some investigators have suggested a causal relation between dietary intake of vitamin B-6 and inflammation (7, 9), but so far no clinical benefit has been found for rheumatoid patients by increasing vitamin B-6 intake (10, 11).

Functional vitamin B-6 status as measured by plasma homocysteine after a methionine load and urinary xanthurenic acid (XA) after a tryptophan load have been investigated in RA patients. Both were found to be increased and inversely correlated with plasma PLP (2).

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Recently, the 3-hydroxykynurenine (HK): XA ratio (HK: XA) in plasma was proposed as a functional marker of vitamin B-6 (12). It represents a substrate-product ratio for the PLP-dependent enzyme, kynurenine aminotransferase, and may reflect intracellular availability of PLP (12). Plasma HK: XA shows a strong, inverse correlation with PLP, moderate correlation with CRP, and weak or no association with kidney function and circulating tryptophan (12). HK and XA are metabolites from tryptophan catabolism along the kynurenine pathway. Activity of the kynurenine pathway and its metabolites have been associated with disease activity in RA patients (13, 14), but have also shown immunomodulatory effects in mouse models of RA (15, 16).

RA is traditionally treated with a variety of medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional disease modifying antirheumatic drugs (DMARDs), and biological DMARDs. The most contemporary biological DMARDs are TNFα inhibitors, which are typically recommended in severe cases or when initial treatment with conventional DMARDs is not effective (17).

The aim of the present study was to investigate vitamin B-6 status, as reflected by plasma PLP and HK: XA, in relation to clinical disease parameters, ultrasonography scores, and established inflammatory markers at baseline and to evaluate changes in vitamin B-6 status after 3 mo treatment with TNFα inhibitors.

Methods

Study population

A longitudinal study was designed, including a total of 106 patients. Patients were recruited at 2 hospitals in Norway, Diakonhjemmet Hospital in Oslo and Haukeland University Hospital in Bergen. Patients fulfilled the American College of Rheumatology/European League Against Rheumatism (EULAR) 2010 criteria for RA (18), and were recruited consecutively during the period 2013–2015 as the treating rheumatologist decided the patient required treatment with a TNFα inhibitor. Participants were initially treated with 1 of the TNFα inhibitors, infliximab (3 mg/kg at 0, 2, and 6 wk, then every 8 wk thereafter), etanercept (50 mg/wk), adalimumab (40 mg/2 wk), golimumab (50 mg/mo), or certolizumab (400 mg at 0, 2, and 4 wk, then 200 mg/2 wk).

Eligible patients were aged between 18 and 75 y, not previously treated with a biological DMARD, had normal liver and renal function, no psychiatric disorders and no other major comorbidities or contraindications for therapy with TNFα inhibitors. Pregnant or nursing females were not included.

Clinical evaluation and collection of blood from the participants were performed at baseline and after 3 mo treatment with TNFα inhibitors.

Ethical approval of the protocol was granted by the Regional Committee on Medical Research Ethics, and written informed consent was obtained from all the participants. The study was registered at helseforskning.etikkom.no with reference number 2011/490.

Clinical data

Disease activity was clinically assessed with use of a composite measure, Disease Activity Score for 28 standard joints (DAS28). DAS28 was calculated based on number of swollen joints, number of tender joints, the patient's own evaluation of disease activity by visual analogue scale (VAS100), and CRP (19).

Ultrasonography scores were based on black mode and power doppler ultrasonography. A summary score was calculated by adding the score from 32 joints, each rated between 0 and 3 according to severity of inflammation (20, 21).

Response to treatment with TNFα inhibitors was evaluated according to EULAR response criteria (19). Patients with a reduction in DAS 28 >1.2 were classified as good responders if the attained DAS28 after 3 mo was ≤3.2, and moderate responders otherwise. Patients with a reduction in DAS28 of >0.6 ≤1.2 were classified as moderate responders if the attained DAS28 after 3 mo was ≤5.1 All other patients were classified as nonresponders.

Participants with plasma cotinine concentration >85 nM at baseline were classified as smokers, whereas those with cotinine below this cutoff were considered to be nonsmokers (22).

Laboratory analysis

Blood samples were collected in EDTA tubes, centrifuged within 2 h, and stored at −80°C until analysis. Samples were shipped on dry ice to the laboratory. Analysis of plasma concentrations of PLP, HK, XA, cotinine (23), and creatinine (24) was performed by Bevital AS, Bergen (www.bevital.no) through use of LC-MS/MS, with within-day CV of 2.3–9.5% and between-day CVs of 2.2–16.9%.

CRP, anticyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF) were analyzed locally: CRP by immunoturbidimetry in Bergen and Oslo (Cobas 6000/8000, Roche Diagnostics, CV: 5%); anti-CCP by multiplex assay (Bioplex 2200, BioRad, CV: 4.3–7.2%) in Bergen and by fluorescent enzyme immunoassay (Phadia 250, Thermo Fisher Scientific, CV: 12%) in Oslo; RF by nephelometry (BN ProSpec, Siemens, CV: 3.8–8.1%) in Bergen and by in-house enzyme-linked immunosorbent assay (25) (CV: 14–16%) in Oslo.

Statistical analysis

Clinical data and amounts of biomarkers are given as medians (25th–75th percentiles). For all parametric statistical tests, clinical data and vitamin/metabolite concentrations were log-transformed. Differences between the 2 centers, Oslo and Bergen, were evaluated by independent Student's *t* test for continuous variables and Pearson's chi-square test for discrete variables. Partial Spearman correlations of clinical parameters with vitamin B-6 markers, adjusted for age, gender, study center, and creatinine, were calculated at baseline.

Change in disease markers and vitamin B-6 markers were calculated as ratios of values at 3 mo divided by values at baseline. Thus, a ratio >1 represents an increased value, and a ratio <1 represents a decreased value following treatment.

To explore relations between change in vitamin B-6 markers (PLP and HK: XA) and change in clinical score (DAS28), generalized additive models (GAMs) analysis was performed through use of the mgcv package in R version 3.13 for Macintosh (26).

In addition, changes in vitamin B-6 markers according to treatment response categories (EULAR response criteria) were evaluated by linear regression analysis with change in PLP or HK: XA as dependent variable and response group (no response 0, moderate response 1, and good response 2) as predictor. Change within the respective groups was assessed by estimated marginal means and 95% CI derived from regression analysis.

Differences across strata, for example, between Oslo and Bergen subcohorts or between age groups, were assessed by including an interaction term (product term) in multiple linear regression models.

Except for GAMs, all statistical analyses were performed with IBM SPSS Version 24 for Windows.

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Supplemental Table 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.
Address correspondence to AU (e-mail: Arve.Ulvik@uib.no).
Abbreviations used: CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, Disease Activity Score for 28 standard joints; DMARD, disease modifying anti-rheumatic drug; EULAR, European League Against Rheumatism; GAM, generalized additive model; HK, 3-hydroxykynurenine; NSAID, nonsteroidal anti-inflammatory drug; PLP, pyridoxal 5′-phosphate; RA, rheumatoid arthritis; RF, rheumatoid factor; VAS100, visual analogue scale scored 0–100; XA, xanthurenic acid.

Results

Characteristics of the study population

The characteristics of the study population at baseline are shown in Table 1. A total of 106 participants was recruited. Median age was 54 y and 36% of the participants were men. Methotrexate was the most common conventional DMARD (84%). Fifty-five percent of patients were currently on therapy with prednisolone, with a median (range) daily dose of 5 mg (2.5–25 mg).

Clinical parameters and biomarkers at baseline

Patients recruited in Bergen had higher disease activity at baseline, with higher values for DAS28, number of tender joints, patient's own evaluation score (VAS100), and CRP (all $P \leq 0.04$, Table 1) than patients from Oslo. Patients from Bergen also had significantly higher values of HK: XA ($P < 0.001$, Table 1). No other variables were found to be significantly different between the 2 recruitment centers. The differences in DAS28 and HK: XA across centers remained significant after adjustment for gender, smoking, steroid usage, and DMARD ($P < 0.001$ by multiple linear regression, data not shown).

PLP was negatively correlated with CRP and black mode ultrasonography score (both $P \leq 0.04$, Table 2), whereas HK: XA was positively correlated with CRP and all clinical parameters and ultrasonography scores (all $P \leq 0.02$, Table 2).

Effect of treatment on disease markers and vitamin B-6 markers

After 3 mo treatment with TNFα inhibitors, geometric means for clinical scores, ultrasonography scores, and CRP were considerably reduced (all $P < 0.001$, **Supplemental Table 1**). Geometric mean PLP was significantly increased by 16% ($P = 0.003$, Supplemental Table 1), but HK: XA showed no significant overall change. Geometric mean DAS28 was reduced by 33% ($P < 0.001$, Supplemental Table 1). Regression analyses showed that the change in DAS28 at 3 mo was not dependent on baseline PLP ($P = 0.44$), or type of TNFα treatment ($P = 0.38$), but was slightly larger for younger patients ($P = 0.08$ by linear regression) and for the Bergen subcohort (39% compared with 28%, $P = 0.03$).

GAM curves, including all the participants, showed that the reduction in DAS28 was positively related to the change in PLP (ß = −0.28, $P = 0.01$) and inversely related to the change in HK: XA (ß = 0.33, $P < 0.001$). The relations were linear for both PLP and HK: XA (**Figure 1**). The majority (87%) of participants experienced reduced DAS28 and increased PLP, but no significant overall change in HK: XA. There

TABLE 1 Baseline characteristics of RA patients before initiating treatment with a TNFα inhibitor[1]

	Center			
	All	Oslo	Bergen	*P* value[2]
N	106	59	47	
Age, y	54 (44–60)	52 (44–61)	54 (45–60)	
Men, *n* (%)	38 (36%)	15 (25%)	23 (49%)	0.01
Smokers, *n* (%)[3]	44 (42%)	23 (39%)	21 (45%)	0.55
DMARDs, *n* (%)	—	—	—	
No DMARD	8 (8%)	3 (5%)	5 (11%)	0.41
Methotrexate	89 (84%)	52 (88%)	37 (79%)	0.41
Other[4]	9 (9%)	4 (7%)	5 (11%)	0.41
Corticosteroids, *n* (%)	—	—	—	
No steroids	48 (45%)	32 (54%)	16 (34%)	0.04
Prednisolone	58 (55%)	27 (46%)	31 (66%)	0.04
Clinical data	—	—	—	
DAS28	3.9 (3.1–4.6)	3.4 (2.7–4.1)	4.3 (3.5–5.3)	0.001
Tender joints 28	3 (1–8)	2 (1–5)	5 (2–13)	<0.001
Swollen joints 28	4 (2–8)	4 (2–8)	4 (3–8)	0.89
VAS100	45 (21–63)	39 (18–55)	50 (31–69)	0.04
BM US score	26 (16–34)	26 (18–35)	22 (11–33)	0.17
PD US score	8 (4–18)	9 (4–19)	7 (4–17)	0.20
Biochemical data	—	—	—	
Serum anti-CCP positive, *n* (%)	83 (78%)	46 (78%)	37 (79%)	0.93
Serum RF positive, *n* (%)	72 (68%)	41 (70%)	31 (66%)	0.70
Serum CRP, μg/L	6 (2–15)	5 (2–9)	9 (3–20)	0.04
Plasma PLP, nmol/L	42 (28–71)	48 (28–71)	39 (27–72)	0.51
Plasma HK: XA	3.0 (2.3–4.0)	2.5 (2.1–3.4)	3.5 (2.6–5.0)	<0.001
Plasma HK, nmol/L	40 (33–48)	38 (31–47)	40 (36–50)	0.13
Plasma XA, nmol/L	13 (10–18)	14 (11–21)	12 (8–16)	0.004

[1] Values are median (25th–75th percentiles) unless otherwise indicated. BM US, black mode ultrasound; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, disease activity score for 28 standard joints calculated with CRP; DMARD, disease modifying antirheumatic drugs; HK: XA, 3-hydroxykynurenine: xanthurenic acid ratio; PD US, power doppler ultrasound; PLP, pyridoxal 5′-phosphate; RA, Rheumatoid arthritis; RF, rheumatoid factor; VAS100, visual analogue scale for pain scored 0–100.

[2] *P* values for differences between centers were determined by Pearson's chi-square test for discrete variables and independent Student's *t* test for log-transformed continuous variables.

[3] Individuals with plasma cotinine concentrations >85 nM were considered to be smokers.

[4] Sulfasalazine, leflunomide, or hydroxychloroquine.

TABLE 2 Spearman correlations of vitamin B-6 markers with disease markers in RA patients at baseline[1]

	PLP		HK: XA	
	ρ	*P* value	ρ	*P* value
DAS28	−0.17	0.09	0.46	<0.001
Tender joints	−0.05	0.62	0.30	0.003
Swollen joints	−0.03	0.76	0.23	0.02
VAS100	−0.12	0.22	0.39	<0.001
BM US score	−0.20	0.04	0.29	0.003
PD US score	−0.14	0.15	0.35	<0.001
Serum CRP	−0.27	0.007	0.36	<0.001

[1] Correlations were adjusted for gender, age, center, and creatinine. BM US, black mode ultrasound; CRP, C-reactive protein; DAS28, disease activity score for 28 standard joints calculated with CRP; HK: XA, 3-hydroxykynurenine: xanthurenic acid ratio; PD US, power doppler ultrasound; PLP, pyridoxal 5′-phosphate; RA, rheumatoid arthritis; VAS100, visual analogue scale for pain scored 0–100.

was, however, a clear tendency of reduced HK: XA among the participants with the greatest improvement in DAS28. A minority (9.4%) of participants experienced an increase in DAS28, which was associated with reduced PLP and increased HK: XA. Association of vitamin B-6 markers with DAS28 was similar for the Oslo and Bergen cohorts (*P*-interaction for PLP, 0.17; for HK: XA, 0.26).

Changes in clinical data and biomarkers during treatment were compared between different EULAR response groups (Table 3, Supplemental Table 1). We found significant changes for vitamin B-6 markers, with increase in PLP (*P*-trend = 0.006) and reduction in HK: XA (*P*-trend = 0.002) according to no, moderate, and good response to treatment. PLP increased significantly by 31% ($P = 0.003$) and HK: XA decreased by 11% ($P = 0.1$) for good responders, whereas HK: XA increased significantly by 25% ($P = 0.02$) for nonresponders.

Notably, although both vitamin B-6 markers changed during treatment, their interrelation remained: At baseline and after 3 mo the correlation between PLP and HK: XA was of similar strength (Spearman's ρ of −0.40, and −0.38, respectively). Moreover, the change in PLP correlated with the change in HK: XA ($\rho = -0.44$) (all $P < 0.001$).

Discussion

Principal findings

PLP was mainly related to CRP at baseline, whereas HK: XA correlated strongly with all markers of disease activity and inflammation. After 3 mo treatment with TNFα inhibitors, clinical parameters were improved for the majority of participants. Both PLP and HK: XA showed improvement in vitamin B-6 status according to improvement in DAS28, a finding corroborated

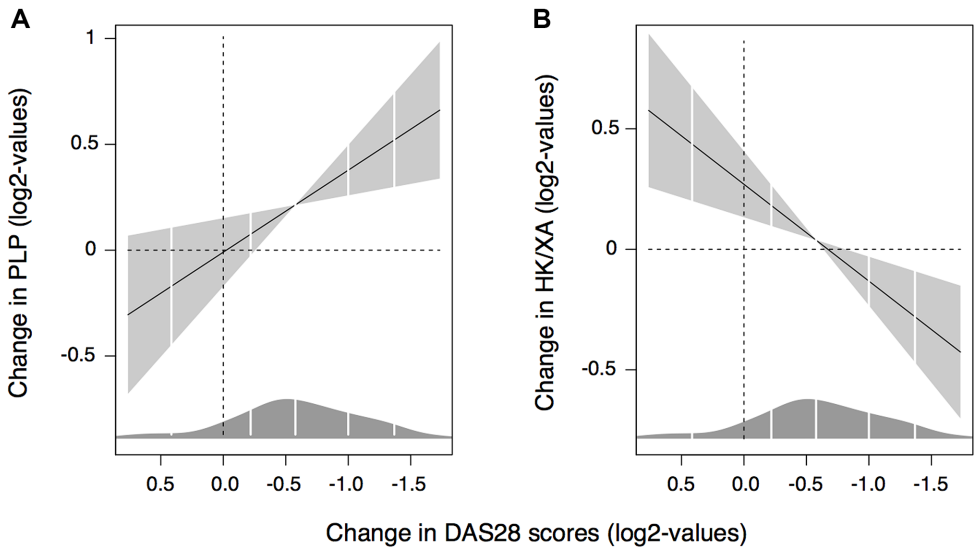

FIGURE 1 Relations of change in DAS28 and change in PLP (A) and HK: XA (B) by generalized additive models in RA patients ($n = 106$) after 3 mo treatment with TNFα inhibitors. Change was assessed by log2-transformed ratios between values at 3 mo divided by values at baseline. Thus, positive values represent an increased value, whereas negative values represent a decreased value following treatment. The points of no change (0 on the scale) are marked with dotted lines. Shaded areas indicate 95% CI. Mean change for PLP and HK: XA are found where the lines for the 95% CI cross each other. A density plot for the distribution of DAS28 is included in each diagram. The y-axes span 2.5 SD of each outcome variable. DAS28, disease activity score for 28 standard joints calculated with CRP; PLP, pyridoxal 5′-phosphate; HK: XA, 3-hydroxykynurenine: xanthurenic acid ratio; RA, rheumatoid arthritis.

TABLE 3 Change in clinical data and biomarkers in RA patients after 3 mo treatment with TNFα inhibitors according to EULAR response groups[1]

	EULAR response[2]			
	No response ($n = 25$)	Moderate response ($n = 36$)	Good response ($n = 45$)	P-trend[3]
DAS28	1.07 (1.00–1.16)	0.71 (0.66–0.75)	0.49 (0.46–0.52)	<0.001
Tender joints 28	1.75 (1.26–2.44)	0.56 (0.42–0.73)	0.25 (0.20–0.32)	<0.001
Swollen joints 28	0.93 (0.67–1.31)	0.44 (0.33–0.58)	0.23 (0.18–0.29)	<0.001
VAS100	0.70 (0.44–1.10)	0.27 (0.18–0.39)	0.21 (0.15–0.30)	<0.001
BM US score	0.76 (0.59–0.99)	0.58 (0.47–0.72)	0.46 (0.38–0.56)	0.003
PD US score	0.80 (0.53–1.21)	0.37 (0.27–0.53)	0.25 (0.18–0.33)	<0.001
Serum CRP	0.68 (0.42–1.11)	0.53 (0.36–0.80)	0.22 (0.16–0.32)	<0.001
Plasma PLP	0.93 (0.76–1.12)	1.16 (0.99–1.36)	1.31 (1.14–1.52)	0.006
Plasma HK: XA	1.25 (1.05–1.48)	1.06 (0.92–1.22)	0.89 (0.79–1.01)	0.002

[1]Change is defined as the ratio of the value at 3 mo divided by the value at baseline. Ratios >1 represent an increased value after treatment and ratios <1 represent a decreased value after treatment. Data are estimated marginal means (95% CI) from a linear regression model with EULAR categories as predictor. BM US, black mode ultrasound; CRP, C-reactive protein; DAS28, disease activity score for 28 standard joints calculated with CRP; EULAR, European League Against Rheumatism; HK: XA, 3-hydroxykynurenine: xanthurenic acid ratio; PD US, power doppler ultrasound; PLP, pyridoxal 5′-phosphate; RA, rheumatoid arthritis; VAS100, visual analogue scale for pain scored 0–100.
[2]Patients with a reduction in DAS28 >1.2 were classified as good responders if the attained DAS28 after 3 mo was ≤3.2, and moderate responders otherwise. Patients with a reduction in DAS28 of >0.6 ≤1.2 were classified as moderate responders if the attained DAS28 after 3 mo was ≤5.1 All other patients were classified as nonresponders.
[3]For calculating P-trend, EULAR categories were entered as a continuous variable.

by similar trends for PLP and HK: XA across the EULAR response categories of no response, moderate response, and good response.

Strengths and weaknesses

The main strengths of the current study are the use of a longitudinal study design, the collection of large amounts of clinical data, and the use of 2 different vitamin B-6 markers to assess vitamin B-6 status. To the best of our knowledge, this is the first study to describe the effect of treatment with TNFα inhibitors on vitamin B-6 status and its relation to clinical outcome in RA patients.

A possible weakness is the recruitment of participants from 2 different centers. The 2 populations showed significant differences at baseline, which may reflect variations in clinical practice regarding initiation of treatment with biological DMARDs. However, DAS28 improvement and change in vitamin B-6 markers were essentially similar across the 2 study centers.

We did not have access to nutritional data or information on the use of vitamin B-6 supplements among the participants. Information on use of NSAIDs was not available. As NSAIDs can cause a reduction in PLP (27), we cannot exclude that discontinuation of NSAID during the 3-mo follow-up period may have affected plasma PLP at 3 mo.

Vitamin B-6 in RA

We observed an inverse association between plasma PLP and markers of disease severity, which is in agreement with observations made by others (1, 3). In RA patients with low PLP, erythrocyte PLP and the erythrocyte aspartate aminotransferase activity coefficient have been reported to be normal, suggesting no PLP reduction in red blood cells from RA patients (1, 2). Experimental studies in rats demonstrated that adjuvant arthritis reduced plasma and liver PLP, but caused no change in PLP in muscle, suggesting that PLP depletion is confined to certain compartments such as serum and liver (4). Reduced liver PLP does not seem to reflect increased vitamin B-6 catabolism, because no change in urinary 4-pyridoxic acid excretion was demonstrated in RA patients or rats with adjuvant arthritis (4).

The functional marker of vitamin B-6 status, HK: XA, showed an even stronger association with markers of disease severity than plasma PLP. This observation points to impaired intracellular vitamin B-6 status affecting the flux through the PLP-dependent kynurenine aminotransferase in RA patients. Impaired functions of PLP-dependent pathways are in agreement with results from published studies on methionine and tryptophan loading in RA patients (2).

Vitamin B-6 markers and treatment with TNFα inhibitors

TNFα inhibitors affect both plasma PLP and HK: XA in the direction of improved vitamin B-6 status in patients with favorable response to treatment. Improved vitamin B-6 status may be related to reduction of inflammation by TNFα inhibitors, as has been observed for CRP (28), and which is in agreement with associations of changes in plasma PLP and HK: XA with changes in DAS28 during treatment.

We observed no overall reduction in HK: XA during treatment, in fact values were increased in patients with no response according to the EULAR criteria. Notably, this subgroup also had a significant increase in Tender joints 28, a trend towards increased DAS28, but a nonsignificant reduction in Swollen joints 28, black mode ultrasonography score, power doppler ultrasonography score, and CRP.

Implications

The clinical significance of impaired vitamin B-6 status in RA patients is presently uncertain. Previous trials of vitamin B-6 supplementation to RA patients have not shown any clinical benefits (10, 11), even though 1 study showed reduced circulating TNFα and IL-6 (11). However, about one-quarter of patients, mainly treatment nonresponders, experienced a possible deterioration of functional vitamin B-6 status (as indicated by increased HK: XA). Thus it may be hypothesized that vitamin B-6 intervention specifically targeted to this subgroup

could improve treatment response or prevent unwanted side effects.

Conclusion

At baseline, the severity of RA was associated with vitamin B-6 markers, most pronounced for the functional vitamin B-6 marker, HK: XA. After 3 mo treatment with TNFα inhibitors, improvement of vitamin B-6 status was dependent on response to treatment, with corresponding and corroborating associations for both PLP and HK: XA. Our findings highlight the relevance of monitoring vitamin B-6 status during treatment with TNFα inhibitors. The strong associations of HK: XA with disease severity and treatment response, link the kynurenine pathway to both disease activity and vitamin B-6 status in RA patients. This should motivate future studies, which should include other metabolites of the kynurenine pathway for their possible involvement in RA.

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