Invited commentary

Vitamin B$_6$ status and requirements in older adults

Vitamin B$_6$ has sometimes been referred to as a 'vitamin without a deficiency'. Non-specific clinical symptoms and functional losses, such as compromised haem synthesis, immunocompetence and electroencephalographic (EEG) abnormalities, have been observed in experimental (depletion) studies, but 'spontaneous' cases of clinical vitamin B$_6$ deficiency in man are rare (for review, see Leklem, 1991; Bender, 1992). Biochemical evidence for an inadequate vitamin B$_6$ supply, such as low plasma pyridoxal phosphate (PLP) levels, has been reported, however, in several studies and for various groups, but especially in elderly (van der Wielen *et al.* 1996; Brussaard *et al.* 1997). Whether the higher prevalence of a marginal vitamin B$_6$ status among elderly has indeed functional consequences, and reflects inadequate intake, or results from metabolic changes resulting in increased vitamin B$_6$ needs, is still under debate. Depletion–repletion studies among elderly males and females by Ribaya-Mercado *et al.* (1991) indeed showed that more vitamin B$_6$ was needed to normalize plasma PLP and tryptophan loading test results compared with results found in similar (earlier) studies with younger adults. Based upon these data, the panel on 'Folate and other B-vitamins' from the Food and Nutrition Board in the USA recently recommended a higher RDA for vitamin B$_6$ for older adults (51+) compared with younger age groups.

In this issue, Bates *et al.* (1999) confirm these findings of low plasma PLP in the elderly in a representative sample of British older (65+) males and females. They also measured plasma 4-pyridoxic acid (4-PA), a catabolic product of vitamin B$_6$, and observed a clear increase of 4-PA with age, which was not solely caused by renal impairment. In this study, as in most other studies, a strong correlation between dietary vitamin B$_6$ intake and plasma PLP was established; however, the mean intake as such was considered adequate, with only 2–3 % of individuals with intakes below the lower nutrient reference intake (LNRI).

The increase in (relative) 4-PA excretion, indicative of a higher catabolic rate, has been reported earlier (e.g. Lee & Leklem, 1985), but is not found in all studies (Kant *et al.* 1988; Pannemans *et al.* 1994). In livers of ageing (female) rats, an age-related increase in pyridoxal (PL) oxidase (*EC* 1.2.3.8) and dehydrogenase (*EC* 1.1.1.107) activities has been found which may result in an increased flux of PL through this oxidative pathway (Bode *et al.* 1991). The availability of PL, i.e. the substrate for 4-PA formation, is regulated by the extent of PLP binding by (enzyme-) proteins. Protein-bound PLP is protected from hydrolysis by alkaline phosphatase (*EC* 3.1.3.1; AP). When the protein-binding capacity decreases, the pool of unbound ('free') PLP increases, resulting in higher PL concentrations. Two enzymes compete for substrate PL: PL-oxidase,

resulting in irreversible oxidation to 4-PA, and PL-kinase (*EC* 2.7.1.35), resulting in (re)phosphorylation to PLP. These mechanisms explain the decrease in 4-PA excretion if protein intake is increased under conditions of an equal vitamin B$_6$ intake. A higher protein intake will result in an increased protein turnover and protein catabolic rate associated with a subsequent increase in transaminase enzyme activity, resulting in an increase in PLP-binding capacity. Actually, 4-PA is a spill-over product, and 4-PA excretion increases when vitamin B$_6$ supply is in excess of PLP-binding capacity. Based upon biokinetic studies in ageing rats, Bode & van den Berg (1991) speculated that the lower plasma PLP levels, and the age-associated increase in 4-PA excretion, might reflect changes in the slowly exchanging vitamin B$_6$ body pools, i.e. in muscle PLP disposition.

Approximately 80 % of the vitamin B$_6$ body store is located in (striated) muscle tissue as PLP bound to glycogen phosphorylase (*EC* 2.4.1.1.). Ageing is generally associated with a decrease in lean body mass, which is mainly muscle tissue, and may consequently result in a decrease in the vitamin B$_6$ body pool. Pannemans *et al.* (1994) investigated the age-dependent relationship between vitamin B$_6$ status indicators and protein turnover by comparing the response of various vitamin B$_6$ status indicators between a group of young (29 (SD 1) years) and elderly (70 (SD 1) years) adults fed on standardized diets containing 12 and 21 % of energy as protein respectively. Plasma PLP was significantly lower for the older, compared with the younger age group in both diet periods. Remarkably, plasma PLP levels were higher on the high-protein compared with the lower-protein diet in the older age group, while there was no effect of protein intake level on plasma PLP in the young adults. In the younger age group, 4-PA excretion indeed became lower on the high-protein diet; however, the reverse effect was seen in the elderly group. Although there was a tendency for a negative correlation between protein breakdown and plasma PLP in the elderly, correlations between protein turnover and indices of vitamin B$_6$ status were not significant. From these data it can be concluded that there is indeed a difference in protein intake-related vitamin B$_6$ needs whereby elderly subjects apparently need less vitamin B$_6$ at a higher protein intake compared with the younger adults. A higher vitamin B$_6$ catabolic rate in the elderly might thus be interpreted as indicative for an increased vitamin B$_6$ need, but could also reflect reduced PLP-binding capacity, i.e. lower body needs. More studies are clearly needed to unravel these complex interactions between vitamin B$_6$ biokinetics and protein turnover in the elderly.

In spite of this ambiguous interpretation of the age-related changes in vitamin B$_6$ metabolism, functional indicators suggest an apparently higher vitamin B$_6$ need in the

elderly. In the study from Bates *et al.* (1999), plasma PLP levels were inversely correlated with plasma homocysteine, an independent risk factor for cardiovascular disease. A similar relationship was reported earlier by Selhub *et al.* (1993). Although folate appears to be the most important determinant of homocysteine levels, and vitamins B_6 and B_{12} of only secondary importance, the repeated finding of a relationship between hyperhomocystinaemia and vitamin B_6 status and intake in the elderly may reflect a suboptimal vitamin B_6 supply. It should be noted, however, that vitamin B_6, contrary to folate supplementation, has not been shown to result in homocysteine lowering, except in rare cases of congenital cystathionine synthase deficiency, nor is there as yet any evidence for a protective effect of vitamin B_6 supplementation on cardiovascular disease risk from controlled intervention trials (Ubbink *et al.* 1994). The reported effects of vitamin B_6 supplementation in elderly subjects on maintenance of an adequate immune response (Meydani *et al.* 1991) and the association with cognitive performance (Riggs *et al.* 1996) also stress the importance of vitamin B_6 adequacy in the elderly. It may therefore turn out that this vitamin 'without a deficiency' has indeed protective effects beyond known functions, but needs more appropriate markers to define optimal intake and adequacy.

H. van den Berg
TNO Nutrition and Food Research Institute
PO Box 360
3700 AJ Zeist
The Netherlands

References

Bates CJ, Pentieva KD, Prentice A, Mansoor MA & Finch S (1999) Plasma pyridoxal phosphate and pyridoxic acid in a representative sample of British men and women aged 65 years and over and their relationship to plasma homocysteine. *British Journal of Nutrition* **81**, 191–201.

Bender DA (1992) In *Nutritional Biochemistry of the Vitamins*, pp. 223–268. Cambridge: Cambridge University Press.

Bode W, Mocking JAJ & van den Berg H (1991) Influence of age and sex on vitamin B_6 vitamer distribution and on vitamin B_6 metabolizing enzymes in Wistar rats. *Journal of Nutrition* **121**, 318–329.

Bode W & van den Berg H (1991) Pyridoxal-5′-phosphate and pyridoxal biokinetics in aging Wistar rats. *Experimental Gerontology* **26**, 589–599.

Brussaard JH, Löwik MRH, van den Berg H, Brants HAM & Kistemaker C (1997) Micronutrient status, with special reference to vitamin B_6. *European Journal of Clinical Nutrition* **51**, Suppl. 3, S32–S38.

Kant AK, Moser-Vellon PB & Reynolds RD (1988) Effect of age on changes in plasma, erythrocyte and urinary B_6 vitamers after an oral vitamin B_6 load. *American Journal of Clinical Nutrition* **48**, 1284–1290.

Lee CM & Leklem JE (1985) Differences in vitamin B_6 status indicator responses between young and middle-aged women fed constant diets with two levels of vitamin B_6. *American Journal of Clinical Nutrition* **42**, 226–234.

Leklem JE (1991) In *Handbook of Vitamins*, 2nd ed., pp. 341–392 [LJ Machlin, editor], New York: Marcel Dekker Inc.

Meydani SN, Ribaya Mercado JD, Russell RM, Sayhoun N, Morrow FD & Gershoff SN (1991) Vitamin B_6 deficiency impairs interleukin 2 production and lymphocyte proliferation in elderly adults. *American Journal of Clinical Nutrition* **53**, 1275–1280.

Pannemans DLE, van den Berg H & Westerterp KR (1994) The influence of protein intake on vitamin B_6 metabolism differs in young and elderly humans. *Journal of Nutrition* **124**, 1207–1214.

Ribaya Mercado JD, Russell RM, Sayhoun N, Morrow FD & Gershoff SN (1991) Vitamin B_6 requirements of elderly men and women. *Journal of Nutrition* **121**, 1062–1074.

Riggs KM, Spiro A III, Tucker K & Rush D (1996) Relations of vitamin B_{12}, vitamin B_6, folate, and homocysteine to cognitive performance in the Normative Aging Study. *American Journal of Clinical Nutrition* **63**, 306–314.

Selhub J, Jacques PF, Wilson PWF, Rush D & Rosenberg IH (1993) Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *Journal of the American Medical Association* **270**, 2693–2698.

Ubbink JB, Vermaak WJH, van der Merwe A, Becker PJ, Delport R & Potgieter HC (1994) Vitamin requirements for the treatment of hyperhomocysteinemia in humans. *Journal of Nutrition* **124**, 1927–1933.

van der Wielen RPJ, Lowik MRH, Haller J, van den Berg H, Ferry M, van Staveren WA (1996) Vitamin B_6 malnutrition among elderly Europeans: The SENECA Study. *Journal of Gerontology* **51A**, B417–B424.