The response to treatment of subclinical thiamine deficiency in the elderly[1–3]

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ABSTRACT The significance of subclinical thiamine deficiency in the elderly was determined by assessing response to thiamine supplementation in a randomized double-blind, placebo-controlled trial. Thirty-five of 222 people aged ≥ 65 y had two concentrations of erythrocyte thiamine pyrophosphate (TPP) < 140 nmol/L 3 mo apart and 41 other people had the first, but not the second, TPP concentration below this value. Both groups were randomly assigned in a double-blind trial to oral thiamine (10 mg/d) or a placebo. All subjects randomly assigned to receive thiamine showed increases in TPP concentrations compared with control subjects. Only the subjects with persistently low TPP concentrations showed subjective benefits from treatment with improvements in quality of life (measured on a visual analogue scale; $P = 0.02$) and decreases in systolic blood pressure ($P = 0.05$) and weight ($P < 0.01$) when compared with subjects given placebo. There was a trend toward benefits in sleep and energy ($P = 0.07$). We conclude that a low TPP concentration on two occasions is a better predictor of response to treatment than an isolated measurement. Quality of life was enhanced by providing thiamine supplements. Blood pressure and weight were lower after thiamine supplementation. *Am J Clin Nutr* 1997;66:925–8.

KEY WORDS Thiamine deficiency, thiamine supplementation, elderly, quality of life, sleep, energy, blood pressure

INTRODUCTION

Thiamine is essential for the metabolism of energy and for neural function (1). Overt thiamine deficiency may result in cardiac beriberi, Wernicke encephalopathy, or a peripheral neuropathy. Mild deficiency has been associated with poor sleep, malaise, weight loss, irritability, and confusion but the mechanism of such nonspecific complaints is unknown (1, 2). Elderly people have been found to have lower thiamine concentrations than younger people but signs of overt thiamine deficiency are uncommon (2–5). The significance of this subclinical thiamine deficiency is not clear because the symptoms may overlap with those of coexisting conditions. In addition, earlier thiamine assays were imprecise and could not reliably define subclinical deficiency states (1). This study aimed to detect subclinical thiamine deficiency in an elderly population by using an HPLC assay and to establish its significance by assessing clinical response to thiamine treatment.

SUBJECTS AND METHODS

Erythrocyte thiamine pyrophosphate (TPP) concentrations were determined in 222 people aged ≥ 65 y after approaching 407 people selected randomly from the age register of an urban general practice. No subjects required hospital-level nursing care. Erythrocyte TPP concentrations were measured directly by using an HPLC method unmodified from that described by Warnock (6). In particular, a 4.6 mm × 100 mm Brownlee aminopropyl 5-μm column (Brownlee AS-MP; PE Brownlee, Norwalk, CT) with a Brownlee aminopropyl 5-μm guard (Brownlee AS-GU; PE Brownlee) were used with a 50:50 (vol:vol) methanol:potassium phosphate buffer solvent system and potassium ferricyanide as the oxidizing reagent. Detection was with a Shimadzu fluorescence monitor RF 530 (Shimadzu Corporation, Kyoto, Japan) and excitation-emission wavelengths of 375 and 440 nm. The between-run CV was 8.6% at 532 nmol/L and 12.5% at 270 nmol/L. The lower limit of normal for TPP (140 nmol/L) was the concentration found in the lowest 2.5% of healthy blood donors from the same city. Each subject who had a TPP concentration < 140 nmol/L had this test repeated within 3 mo just before entering the randomization phase. Subjects with low TPP concentrations on both occasions ("persistently" low) were analyzed as a separate subgroup.

Seventy-six of the 96 (79%) subjects with low TPP concentrations participated in a randomized, double-blind treatment trial with either oral thiamine (10 mg/d) or placebo for 3 mo. Randomization was stratified by pretreatment TPP concentration. The following variables were measured before treatment: dominant hand grip strength by using a Preston hand grip dynamometer, weight in ordinary clothes (kg), height without shoes (cm), body mass index (height divided by weight squared in kg/m^2), and blood pressure (mm Hg) by using a mercury sphygmomanometer in the standard manner.

Cognition was assessed by using the 30-point Folstein et al Mini-Mental State Examination (MMSE) (7), in which higher scores indicate better cognition. Functional ability was assessed by

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using the 45-point Frenchay Activities Index (8), in which higher scores indicate the subject is more active. General health was assessed by using the Nottingham Health Profile (NHP), in which lower scores indicate better health status. The NHP consists of a total score and six subscales (energy level, pain, emotional reactions, sleep, social isolation, and physical abilities) and has been validated for use in community-dwelling elderly populations. It is able to discriminate groups differing in diagnosed chronic illness, physiologic fitness, and medical consultation rates (9, 10). A 10-cm visual analogue scale was used to assess overall quality of life in which lower scores indicate better quality of life. The clinical examination, all the above variables, and TPP concentrations were repeated after the 3-mo trial period by using the same methods as at baseline. Compliance was assessed with a pill count at the end of the 3-mo intervention period. Daily alcohol intake was assessed as part of a dietary survey with a validated food-frequency questionnaire (11). The study was approved by the Canterbury Area Health Board Ethics Committee and all patients gave written informed consent.

Chi-square test was used to compare categorical variables. TPP concentrations and changes after treatment were compared by using Student's t test. Analysis of variance was used to make comparisons of baseline measures between the treatment groups. Analysis of covariance was used to determine whether current treatment for hypertension affected the effect of supplementation on blood pressure. Results are expressed as means with 95% CIs.

RESULTS

Demographic data and information on the most common diseases and medications within the study population are shown in **Table 1.** Anthropometric and functional indexes before treatment are shown in **Table 2.** There were no significant differences between those subjects randomly assigned to placebo or to thiamine supplementation. Daily alcohol intake was significantly ($P = 0.02$) higher in subjects with persistently low TPP concentrations [8.1 g/d (95% CI: 3.2, 13.0)] than in those with isolated, low TPP concentrations [2.4 g/d (95% CI: 1.0, 3.9)].

All subjects who were randomly assigned completed the study. Compliance with trial medication was > 95% in all cases. Subjects randomly assigned to active treatment with thiamine for 3 mo showed significant increases in TPP concentrations by a mean of 70 nmol/L (95% CI: 56, 84) compared with 18 nmol/L (95% CI: −2, 38) in those randomly assigned to receive placebo ($P < 0.0001$). Subjects with persistently low TPP concentrations showed subjective effects of treatment (**Table 3**) with improvement in quality of life ($P = 0.02$) and decreases in systolic blood pressure ($P = 0.05$) and weight ($P < 0.01$) when compared with subjects given placebo. The total NHP score showed no change with supplementation (Table 3) but there were trends toward benefit from supplementation as measured by the subscales of energy ($P = 0.07$) and sleep ($P = 0.07$). Subjects with an isolated low TPP concentration given thiamine supplements also tended to lose weight ($P = 0.08$) but showed no other significant changes after intervention (Table 3). Analysis of covariance showed no effect of current treatment for hypertension on the effect of supplementation on blood pressure. There were no significant changes in grip strength, functional ability (8), cognition (7), or any of the other NHP subscales. Fifteen subjects had evidence of sensory neuropathy, one had motor neuropathy, and one had an abnormal result from the Romberg test but thiamine treatment did not result in any clinical alteration in these abnormalities.

DISCUSSION

By definition, patients with subclinical thiamine deficiency are asymptomatic. However, nonspecific subjective symptoms caused by chronic nutritional inadequacy might only become apparent to an individual once they notice an improvement after correction of the deficiency. The measures of improvement used to assess response to supplementation in this study were kept broad so that improvements in overall well-being or quality of life might be detected. We would expect the greatest benefit of supplementation to be seen in people with persistently low concentrations rather than those with just an isolated low concentration. The positive effect of supplementation on quality of life was seen only in

TABLE 1
Demographic, disease, and medication data by randomization group for elderly people with isolated and persistent low thiamine concentrations[1]

	Persistent low thiamine		Isolated low thiamine	
	Supplemented	Placebo	Supplemented	Placebo
Total	18 [51]	17 [49]	20 [49]	21 [51]
Age (y)	73.3 (71.2, 75.5)[2]	76.4 (73.6, 79.3)	76.5 (73.9, 79.1)	73.7 (71.6, 75.7)
Female	10 [56]	9 [53]	12 [60]	11 [52]
Live at home alone	7 [39]	7 [41]	8 [40]	6 [29]
Live at home with others	11 [61]	10 [59]	11 [55]	15 [70]
Live in rest home	0 [0]	0 [0]	1 [5]	0 [0]
Treated for hypertension	4 [22]	5 [29]	7 [35]	6 [29]
Treated for cardiac failure	2 [11]	1 [6]	1 [5]	1 [5]
Ischemic heart disease	5 [28]	5 [29]	1 [5]	1 [5]
Previous stroke	4 [22]	3 [18]	1 [5]	1 [5]
Taking furosemide	3 [17]	1 [6]	2 [10]	1 [5]
Taking thiazide	4 [22]	4 [24]	0 [0]	3 [14]

[1] n; percentage in brackets.
[2] 95% CI in parentheses.

TABLE 2
Baseline data by randomization group for elderly people with isolated and persistently low thiamine concentrations[1]

	Persistently low thiamine		Isolated low thiamine	
	Supplemented (n = 18)	Placebo (n = 17)	Supplemented (n = 20)	Placebo (n = 21)
Alcohol (g/d)	10.7 (2.3, 19.0)	5.4 (−0.3, 11.1)	0.4 (0.1, 0.8)	4.4 (1.8, 7.1)
Body mass index (kg/m^2)	26.0 (24.4, 27.7)	24.4 (22.5, 26.3)	24.4 (22.7, 26.2)	25.2 (23.7, 26.8)
Grip strength (kg)	18.1 (13.1, 23.1)	18.3 (12.5, 24.1)	14.5 (10.5, 18.5)	18.2 (13.4, 23.0)
MMSE	28.3 (25.6, 34.6)	28.6 (27.2, 30.1)	29.3 (28.3, 30.0)	29.8 (29.6, 30.0)
FAI	31.2 (27.7, 34.6)	30.1 (26.4, 33.8)	32.1 (27.7, 36.5)	35.1 (32.1, 38.0)
NHP				
Total score	71.4 (21.9, 121.0)	85.0 (36.8, 133.2)	62.4 (29.8, 95.1)	30.5 (11.2, 49.7)
Energy subscale	23.0 (5.4, 40.5)	24.8 (8.1, 41.6)	13.6 (0, 28.0)	14.4 (0.9, 27.9)
Sleep subscale	26.8 (11.8, 41.8)	18.7 (7.6, 29.8)	25.6 (11.7, 39.4)	18.1 (6.0, 30.0)
Quality of life VAS	72.2 (61.1, 83.3)	72.1 (63.5, 80.7)	73.8 (64.2, 83.3)	77.2 (67.4, 87.0)
Systolic blood pressure (mm Hg)	143.7 (129.9, 157.5)	137.4 (126.8, 147.9)	149.1 (138.4, 159.8)	143.3 (132.2, 154.4)
Weight (kg)	72.3 (67.1, 77.5)	66.5 (59.4, 73.5)	67.8 (62.5, 73.1)	72.0 (65.2, 78.8)

[1] $\bar{x}$: 95% CI in parentheses. Differences between supplemented and placebo groups were not significant. MMSE, Folstein Mini-Mental State Exam [maximum score = 30; higher scores indicate better cognition (7)]; FAI, Frenchay Activities Index [maximum score = 45; higher scores indicate subject more active (8)]; NHP, Nottingham Health Profile [score range = 0–100; lower scores indicate better health status (9, 10)]; VAS, visual analogue scale (score range = 0–100 mm; lower scores indicate better quality of life).

people with persistently low TPP concentrations and therefore supports this expectation. We found no change in scales of cognition or Activities of Daily Living after supplementation but there was a low prevalence of difficulties in these areas so both scales showed considerable "ceiling" effects.

There was the suggestion that energy and sleep might improve after supplementation, although this trend was not significant (P = 0.07). The changes in sleep should be interpreted with particular caution because there were definite (although not significant) differences in the baseline values for this measure. The effect of supplementation could therefore be explained by regression to the mean. These findings are consistent, however, with the symptoms described during experimental thiamine deficiency in humans of poor sleep, irritability, and malaise (1). The only other study examining the effect of thiamine supplementation on noncardiac variables also showed beneficial effects on sleep and energy (2). In that study, thiamine supplements were given in a placebo-controlled fashion to 80 women from a population with marginal thiamine deficiency. Nearly one-third of those women, however, had normal thiamine status as assessed by the less precise erythrocyte transketolase activity (1). Other variables showing improvement in that study were appetite, energy, body weight, and general well-being.

Although erythrocyte concentrations should fluctuate less over time than plasma concentrations, our findings suggest that an isolated low erythrocyte concentration may still not be a reliable indicator of the need for vitamin replacement. Low concentrations on two occasions within 3 mo was a better predictor of potential benefit from supplementation. It also had a better correlation with alcohol intake because people with persistently low TPP concentrations had a higher alcohol consumption than those with an isolated low concentration. In neither group was alcohol consumption excessive, however.

TABLE 3
Effect of thiamine supplementation or placebo in elderly people with an isolated low thiamine concentration and in those with persistently low thiamine concentrations[1]

	Persistently low thiamine			Isolated low thiamine		
	Supplemented (n = 18)	Placebo (n = 17)	P	Supplemented (n = 20)	Placebo (n = 21)	P
Change in Nottingham Health Profile						
Total score	−17.0 (−40.6, 6.5)	7.6 (−17.3, 32.5)	0.13	−8.6 (−42.0, 24.8)	−14.8 (−33.8, 4.1)	0.74
Energy subscale	−5.7 (−17.2, 5.9)	7.4 (−2.1, 16.9)	0.07	7.9 (−3.0, 18.8)	6.9 (−1.7, 15.5)	0.9
Sleep subscale	−9.5 (−15.9, 3.2)	−0.7 (−9.1, 7.7)	0.07	−8.1 (−18.3, 2.0)	−4.4 (−15.0, 6.3)	0.6
Change in quality of life, by visual analogue scale (mm)	−9 (−18, 0)	4 (−2, 10)	0.02	3 (−4, 10)	0 (−6, 6)	0.5
Change in systolic blood pressure (mm Hg)	−6.9 (−19.5, 5.7)	7.6 (−0.9, 16.2)	0.05	−3.4 (−14.6, 7.3)	7.0 (−4.5, 18.5)	0.16
Change in weight (kg)	−1.2 (−2.4, 0.0)	0.6 (−0.1, 1.4)	<0.01	−0.9 (−1.9, 0.0)	0.1 (−0.7, 1.0)	0.08

[1] $\bar{x}$; 95% CI in parentheses. Decreases in Nottingham Health Profile subscales and visual analogue scale indicate improvement.

The cutpoint of 140 nmol/L used in our study was derived from that found in the lowest 2.5% of a healthy blood donor population from the same city. This lower limit of normal, seen in a healthy population, cannot be assumed to be the upper limit of abnormal. The range of concentrations seen in people with diseases normally associated with thiamine deficiency needs to be clarified and cannot be extrapolated from our study. Our findings suggest that there is a syndrome of mild thiamine deficiency that affects quality of life and that is responsive to treatment. This syndrome, affecting people with persistently low TPP concentrations, had a prevalence in our study population of 35/222, or 16%.

People taking furosemide have been shown to have a higher incidence of thiamine deficiency (12) and an improvement in cardiac function after thiamine supplementation (13). Cardiac function can improve rapidly after intravenous thiamine (14). Overt thiamine deficiency, as evidenced by cardiac beriberi, is rare in North America, except among alcoholics. This may be partly because flour and rice are enriched with this vitamin (5). Supplementation of grains with thiamine does not occur in New Zealand.

The differential in supplementation of grains and the variety of methods used to assess thiamine status make it difficult to compare the prevalence of thiamine deficiency in New Zealand with that in the United States. The Boston nutritional status survey showed that 2–5% of elderly subjects were deficient in thiamine and an additional 15% had marginal thiamine status (5). Among subjects taking vitamin supplements, it was estimated that only 5–10% had marginal thiamine status. No subject taking vitamin supplements consumed less than two-thirds of the recommended dietary allowance of thiamine (15). Other dietary surveys of free-living elderly North Americans have shown severe deficiency in $\leq$ 10% and marginal deficiency in $\approx$15% (3). All of these nutritional surveys relied either on dietary intake or some biochemical measure of blood thiamine concentrations. They must therefore be estimates of true thiamine status, because none has examined any changes in clinical variables after supplementation. They indicate, however, that a significant proportion of the US elderly have the potential to benefit from intervention.

Weight and systolic blood pressure showed unexpected reductions after supplementation. We cannot offer a definite explanation for these findings, especially because weight gain was observed in the only other randomized trial of thiamine supplementation (2). We note, however, that if subclinical or mild cardiac failure were improved after thiamine supplementation, then a decrease in weight indicating diuresis might be the earliest index to change. Diuresis and natriuresis were observed when people taking furosemide for heart failure were given intravenous thiamine (13). The effect on systolic blood pressure was unexpected but substantial, with a difference between the supplemented and placebo groups of $>$ 14 mm Hg. These findings require verification because the difference between the placebo and supplemented groups was due, in part, to a small rise in blood pressure for those given placebo. The high prevalence of sensory neuropathy in people with low TPP concentrations observed in this study may be relevant because peripheral neuropathy is a feature of overt thiamine deficiency (3). Thiamine supplementation resulted in no clinical improvement in the neuropathy but the treatment and follow-up period may have been too short to detect any change. In addition, we cannot be certain that the sensory neuropathy observed was directly attributable to thiamine deficiency.

In conclusion, we suggest that a TPP concentration $<$ 140 nmol/L on two occasions is a better predictor of response to treatment than is an isolated measurement. Quality of life was enhanced in this group by providing thiamine supplements. A significant proportion of the community-dwelling elderly population has the potential to benefit from thiamine supplementation or dietary modification. Further study is needed to verify these findings and the effects of supplementation on energy, sleep, cardiac function, blood pressure, and weight.

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REFERENCES

1. Finglas PM. Thiamin. Int J Vitam Nutr Res 1993;63:270–4.
2. Smidt LJ, Cremin FM, Grivetti LE, Clifford AJ. Influence of thiamin supplementation on the health and general well-being of an elderly Irish population with marginal thiamin deficiency. J Gerontol 1991;46:M16–22.
3. Iber FL, Blass JP, Brin M, Leevy CM. Thiamin in the elderly—relation to alcoholism and to neurological degenerative disease. Am J Clin Nutr 1982;36:1067–82.
4. O'Rourke NP, Bunker VW, Thomas AJ, Finglas PM, Bailey AL, Clayton BE. Thiamine status of healthy and institutionalized elderly subjects: analysis of dietary intake and biochemical indices. Age Ageing 1990;19:325–9.
5. Sokoll LJ, Morrow FD. Thiamin. In: Hartz SC, Russell RM, Rosenberg IH, eds. Nutrition in the elderly—The Boston nutritional status survey. London: Smith-Gordon and Company, Limited, 1992:111–7.
6. Warnock LG. The measurement of erythrocyte thiamin pyrophosphate by high-performance liquid chromatography. Anal Biochem 1982;126:394–7.
7. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
8. Wade DT, Legh-Smith J, Hewer RL. Social activities after stroke: measurement and natural history using the Frenchay Activities Index. Int Rehabil Med 1985;7:176–81.
9. Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. J R Coll Gen Pract 1985;35:185–8.
10. Baum FE, Cooke RD. Community-health needs assessment: use of the Nottingham health profile in an Australian study. Med J Aust 1989;150:581–90.
11. Horwath CC. Validity of a short food frequency questionnaire for estimating nutrient intake in elderly people. Br J Nutr 1993;70:3–14.
12. Seligmann H, Halkin H, Rauchfleisch S, et al. Thiamine deficiency in patients with congestive heart failure receiving long-term furosemide therapy: a pilot study. Am J Med 1991;91:151–5.
13. Shimon I, Almog S, Vered Z, et al. Improved left ventricular function after thiamine supplementation in patients with congestive heart failure receiving long-term furosemide therapy. Am J Med 1995;98:485–90.
14. Ikram H, Maslowski AH, Smith BL, Nicholls MG. The haemodynamic, histopathological and hormonal features of alcoholic beriberi. Q J Med 1981;50:359–75.
15. National Research Council. Recommended dietary allowances. 10th ed. Washington, DC: National Academy Press, 1989.