

ORIGINAL ARTICLE

Supplementary Thiamine is Still Important in Alcohol Dependence

Ellen Rees and Linda R. Gowing*

Discipline of Pharmacology, University of Adelaide, Adelaide, South Australia, SA 5005, Australia

*Corresponding author: Tel.: +61-8-8313-8055; E-mail: linda.gowing@adelaide.edu.au

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Abstract — **Aims:** To assess the effect of mandatory thiamine enrichment of wheat flour on blood thiamine levels in an alcohol-dependent population. **Methods:** Alcohol-dependent clients ($n=100$) entering an inpatient service for the management of alcohol withdrawal had thiamine blood tests and diet interviews. Approximately half ($n=46$) the alcohol-dependent participants reported taking vitamin supplements prior to admission. Standard treatment included thiamine supplementation in the form of an intramuscular injection and 100 mg tablets. If consent was gained, a second thiamine blood test was taken prior to discharge ($n=77$). Control participants ($n=20$) with no history of treatment for alcohol abuse had thiamine blood tests and diet interviews. **Results:** Control participants consumed significantly larger amounts of thiamine in their diet compared with alcohol-dependent participants ($P<0.0001$). Alcohol-dependent participants who reported no use of vitamin supplements had significantly lower ($P<0.05$) blood thiamine levels compared with controls, whereas controls and those who reported using vitamin supplements had no significant difference. No significant correlation was found between thiamine blood levels and reported levels of alcohol consumption. **Conclusion:** Reduced blood levels of thiamine in people who are alcohol dependent, compared with those with no history of alcohol abuse, are likely to be because of the poor diet. Consumption of vitamin supplements appears to bring thiamine levels closer to those seen in control participants. Supplementation of dietary intake of thiamine in people who are alcohol dependent remains an important measure for the prevention of Wernicke–Korsakoff's syndrome in this population.

INTRODUCTION

Thiamine is required by all tissues and must be ingested in the diet. Thiamine requirements increase with total calorie intake, when the diet is rich in carbohydrate, and when basal metabolism is increased, such as in alcohol withdrawal (Sechi and Serra, 2007; Mancinelli and Ceccanti, 2009). The Australian National Health and Medical Research Council recommends daily intake of thiamine should be 1.1 mg for women and 1.2 mg for men (based on a requirement of 0.33 mg/kcal consumed). This study used these figures as the recommended daily intake (RDI), but it should be noted that other authorities recommend intake as high as 0.5 mg/kcal consumed (Sechi and Serra, 2007).

After two to three weeks of inadequate intake, thiamine deficiency can occur due to a storage limit in the body of only 25–30 mg (Mancinelli and Ceccanti, 2009). People who are alcohol dependent are prone to thiamine deficiency because of decreased dietary intake and effects of ethanol on thiamine transport, storage, absorption and utilization (Harper, 2006; Mancinelli and Ceccanti, 2009).

Two thiamine specific transport systems have been identified in human tissues that are responsible for carrier-mediated uptake and secretion (Laforenza *et al.*, 1998; Rindi and Laforenza, 2000; Martin *et al.*, 2003; Reidling *et al.*, 2010). These are thiamine transporters 1 (THTR-1) and 2 (THTR-2). THTR-1 is abundantly located on skeletal and cardiac muscle with medium expression in the liver, heart and kidneys. THTR-2 is widely expressed but mainly found on the kidneys, liver and placenta (Dutta *et al.*, 1999).

Ingested thiamine is absorbed primarily in the proximal part of the small intestine through the action of enterocytes (intestinal absorptive cells). At high concentrations, diffusion occurs, but at low concentrations absorption occurs via THTR-1 or -2 (Hoyumpa, 1980; Reidling *et al.*, 2006; Reidling *et al.*, 2010). This active transport mechanism is rate limited (Mancinelli and Ceccanti, 2009). Thiamine is

slowly released into blood plasma from the enterocyte, where 90% is in free-form. Once it enters the blood, the free-form thiamine diffuses into erythrocytes (Rindi and Laforenza, 2000; Martin *et al.*, 2003). The kidneys reclaim filtered thiamine to prevent loss in the urine (Reidling *et al.*, 2006).

Once thiamine enters a cell it is converted to the active form, thiamine diphosphate (TDP) (Hoyumpa, 1980; Martin *et al.*, 2003). TDP is a co-factor for enzymes involved primarily in carbohydrate metabolism (Herve *et al.*, 1995; Harper, 2006; Mancinelli and Ceccanti, 2009). If thiamine levels decrease, the activity of these enzymes also decreases, interfering with cellular function (Martin *et al.*, 2003; Harper, 2006).

Alcohol consumption has been shown to cause transcription-mediated inhibition of THTR-1 and -2 expression (Kiela, 2010; Subramanian *et al.*, 2010; Subramanya *et al.*, 2010), decreases in TDP (Hoyumpa, 1980), reduced liver storage (Thomson *et al.*, 1971; Hoyumpa, 1980) and decreased intestinal absorption (Hoyumpa, 1980; Singleton and Martin, 2001; Martin *et al.*, 2003). Brain disorders such as Wernicke–Korsakoff syndrome (WKS) can result from thiamine deficiency (Sechi and Serra, 2007). WKS is associated with memory dysfunction and characteristic lesions in the thalamus, mamillary bodies and frontal lobe of the brain (Kopelman *et al.*, 2009).

Australia is unique in having a program of mandatory thiamine fortification of bread and wheat flour. The addition of thiamine to cereal grains was mandatory in the USA in the 1940s (Bishai and Nalubola, 2002) but currently the sale of unenriched flour is not prohibited in the USA as long as the product meets labelling requirements. The addition of thiamine to wheat flour at the level of 6.4 mg/kg was made mandatory in Australia in 1991 (Australia New Zealand Food Standards Code, 2009). This was deemed necessary after general population autopsy research showed relatively high prevalence of WKS (4.7%) in Australia (Harper, 1979;

Harper, 1983). Flour enrichment appears to have made a difference, as the prevalence of WKS in autopsies subsequently decreased to 1.1% (Harper *et al.*, 1998). However, there has been little research into the effect of the addition of thiamine to flour on thiamine levels in people abusing alcohol.

In a recent study in South Australia thiamine levels were measured in people attending a clinic for assessment of fitness to drive a motor vehicle (65% with alcohol abuse, 35% alcohol dependent). In this group blood thiamine levels were larger than expected, and significantly higher than a European reference population (Crowley and Gaughwin, 2011). Following on from this study we sought to determine blood thiamine levels in an alcohol-dependent population relative to a comparison group of people with no history of alcohol abuse, to assess changes in thiamine levels in response to thiamine treatment, and to determine factors predictive of blood thiamine levels.

METHODS

Setting

The study was undertaken at a public inpatient unit specialising in drug and alcohol withdrawal (Drug and Alcohol Services, South Australia). Admission to the unit was on a voluntary basis, after preliminary telephone-based assessment by a member of the nursing staff. Clients are generally admitted to the inpatient unit within one to two weeks of requesting withdrawal. Withdrawal is supervised by medical and nursing staff experienced in the management of drug and alcohol dependence. Clients experiencing, or at high risk of complications such as delirium tremens, are referred to a hospital for more intensive care.

Participants

All people entering the inpatient clinic were eligible if they required blood samples taken for routine testing and did not receive intramuscular vitamin treatment before blood was taken. Inclusion criteria were a diagnosis of alcohol dependence based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV), aged between 18 and 65 years old, able to give informed consent and settled into the inpatient unit with no severe withdrawal symptoms. Screening for suitability was based on assessment by clinical staff, medical history, case note review and an interview with the participant. Participants were given an information sheet explaining the study and all procedures. Participants were reimbursed for their time and inconvenience with a \$40 gift voucher redeemable for food or clothing.

Twenty people were recruited for the control group with a gender and age balance similar to the alcohol-dependent participants. Control participants were volunteers from the University of Adelaide and Drug and Alcohol Services South Australia. Inclusion criteria for the control group were the absence of alcohol abuse or dependence, within the age range of 18–65 years, and able to give informed consent.

The study was approved by the Human Ethics Committee of the University of Adelaide, and by Drug and Alcohol Services South Australia.

Alcohol-dependent participants

Alcohol-dependent participants were admitted to the inpatient unit on Day 0 and remained until Day 5 (6 days in total). The length of stay was extended to 7–10 days if significant withdrawal was experienced. Blood samples were taken for routine clinical tests and thiamine assay on admission.

After blood was taken, participants received a single intramuscular injection of 2.5 ml of B Dose Forte, a multi B vitamin complex preparation (Biological Therapies, Victoria, Australia) which contains 100 mg/ml thiamine. Oral thiamine supplementation (100 mg three times a day) as Bitamin (Sanofi Aventis, New South Wales, Australia) was maintained for the duration of inpatient treatment.

On admission participants were assessed for intoxication and withdrawal. Typically a loading dose of diazepam (based on body weight) was administered with further doses given according to withdrawal severity measured by the Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar).

On day two or three participants were approached for formal consent and interviewed about their typical diet, the food they ate in the week before admission, and whether they were using any vitamin supplements at the time of admission. (Participants were not asked about the amount or frequency of consumption of vitamin supplements, or the source of the supplements). Participants were also asked to consent to the taking of a second blood sample. This was taken on day four or five to determine blood thiamine levels at discharge.

Case notes were accessed for information such as age, gender, diabetic status, blood-borne virus status, number of previous treatment episodes, duration of dependence, prescription medications, other drug use, level of alcohol consumption, and blood test results. Alcohol consumption was part of the routine medical assessment undertaken by doctors with experience in addiction treatment using an approach consistent with timeline followback procedure. Information on employment status and income was not recorded, but the majority (>80%) of clients admitted to the inpatient unit are unemployed. Standard blood tests included levels of albumin, bilirubin, gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), magnesium and mean cell volume (MCV). These biomarkers have been shown to have a role in detecting both liver function and thiamine deficiency (Mancinelli and Ceccanti, 2009).

Control group

Participants attended an interview at a location convenient to them. After formal consent they were interviewed about their normal alcohol consumption and typical diet using a daily food record sheet (see below) and information about standard drinks. Participants were also asked whether they used vitamin supplements. Participants attended a pathology service within two days of the interview to have a blood sample taken to test for thiamine levels.

Thiamine tests

Blood thiamine levels were determined by a pathology service following standard procedures using a high-performance

liquid chromatography (HPLC) reagent kit (Chromsystems Instruments and Chemicals, GmbH, Munich, Germany).

Diet analysis

A daily food record sheet was developed to record participants' weekly food intake. Previous studies have used similar approaches to gain dietary information (Krall and Dwyer, 1987; Arroll *et al.*, 1991). The information obtained was entered into McGraw Hill Higher Education Nutrition Calculator Plus. This software allowed for the evaluation of the percentage of RDI of thiamine obtained by participants from their diet, based on the Australian RDI of 1.1 mg for women and 1.2 mg for men.

Statistical analysis

Alcohol-dependent participants were divided into two groups based on whether or not they reported regular use of vitamin supplements prior to admission. All analyses were non-parametric as the data were not normally distributed. All data are presented as the median and range. Results were considered significant if $P < 0.05$.

Admission and discharge thiamine levels were compared with dietary thiamine intake, liver function test results and alcohol consumption using a Spearman correlation analysis. The change in thiamine level (discharge minus admission) was compared with GGT levels using correlation analysis. The change in thiamine concentrations for the group using vitamins prior to admission, and the group not using vitamins, was compared using a Mann–Whitney t -test. All the correlation results were obtained using two-tailed P -values.

A one-way analysis of variance (ANOVA) was used to compare admission and discharge blood thiamine levels in the alcohol-dependent groups with the control group. Dietary intake of thiamine was also compared for the control- and alcohol-dependent groups using a one-way ANOVA. All one-way ANOVAs were analysed using a Kruskal–Wallis test and Dunn's Multiple Comparison test.

RESULTS

Participants

The alcohol-dependent group comprised 100 participants (65 males, mean age 44 years; 35 females, mean age 42 years). Discharge blood samples were collected for 77 of these 100 participants (47 males, 30 females). The median alcohol consumption reported by participants prior to admission was 225 g/day (range 55–800 g/day).

The control group comprised 20 participants (12 males, mean age 44 years; 8 females, mean age 43 years).

Thiamine levels

Admission blood thiamine levels in alcohol-dependent participants who did not take vitamin supplements ($n = 54$, median 161 nmol/l, range 90–337) were significantly lower than blood thiamine levels in the control-group participants ($n = 20$, median 214 nmol/l, range 97–349), as shown in Fig. 1. Blood thiamine levels in alcohol-dependent participants who did take vitamin supplements ($n = 46$, median 187 nmol/l, range 108–383) were lower than blood thiamine

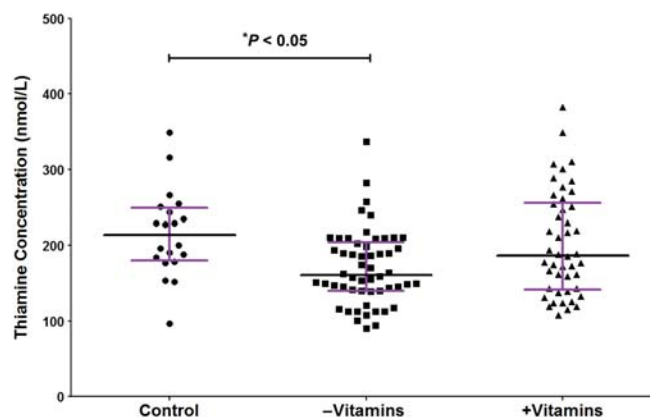


Fig. 1. Blood thiamine levels in alcohol-dependent participants at admission relative to the control-group participants with no history of alcohol abuse. Central line indicates median, bars indicate interquartile range. Admission blood levels in alcohol-dependent participants who did not consume vitamins (–vitamins) were significantly lower ($P = 0.005$) than levels in the control group. The median blood thiamine level for alcohol-dependent participants who reported consuming vitamins (+vitamins) was lower than the median level for the control group but the difference was not statistically significant.

levels in the control-group participants, but the difference was not statistically significant. Admission blood thiamine levels in alcohol-dependent participants who did not take vitamin supplements were significantly lower than levels reported in a previous study (Crowley and Gaughwin, 2011) involving participants predominantly with a diagnosis of alcohol abuse rather than dependence (see Table 1).

No correlation was found between reported levels of alcohol consumption and admission blood thiamine levels. No correlation was found between any of the measures of liver function and admission blood thiamine levels, except for bilirubin. As bilirubin levels increased, admission blood thiamine concentration decreased significantly ($P = 0.005$, $r = -0.29$). Summary blood test results are shown in Table 2.

All alcohol-dependent participants were discharged with blood thiamine levels that were significantly higher than levels in the control group (Table 1). There was no significant correlation between the change in blood thiamine levels and GGT levels, and no significant difference in discharge thiamine levels for those who reported taking vitamin supplements prior to admission and those who did not.

Dietary intake

Dietary thiamine intake (not taking account of thiamine received in supplements) was significantly lower in alcohol-dependent participants compared with the control group (Fig. 2). Alcohol-dependent participants taking vitamin supplements ($n = 46$) were estimated to receive a median 61% (range 17–237%) of the RDI of thiamine from their diet, when compared with 66.5% (range 10–230%) for alcohol-dependent participants not taking vitamin supplements ($n = 54$), and 161.5% (range 100–305%) for the control group ($n = 20$). There was a significant correlation between the RDI of thiamine and admission blood thiamine levels for alcohol-dependent participants not taking vitamin supplements ($P = 0.049$, $r = 0.27$).

Table 1. Summary of blood thiamine levels and estimated percentage of RDI of thiamine obtained from diet

	Control	Alcohol dependent		Alcohol abuse or dependence
		+Vitamin	–Vitamin	
Initial blood thiamine, nmol/l, median (range)	214 (97–349), <i>n</i> = 20	187 (108–383), <i>n</i> = 46	^a 161 (90–337), <i>n</i> = 54	213 (106–362), <i>n</i> = 124
Discharge blood thiamine, nmol/l, median (range)	–	^b 297 (154–506), <i>n</i> = 36	^b 282 (128–412), <i>n</i> = 41	–
% RDI of thiamine from diet, median (range)	161.5 (100–305), <i>n</i> = 20	^c 61 (17–237), <i>n</i> = 46	^c 66.5 (10–230), <i>n</i> = 54	–

Data for the group with alcohol abuse or dependence were obtained from a previous study (Crowley and Gaughwin, 2011).

^aThiamine level significantly lower than the control group, and group with alcohol abuse or dependence.

^bThiamine levels significantly higher than baseline.

^cRDI significantly lower than the control group.

Table 2. Summary of blood test results (other than thiamine) for alcohol-dependent participants at admission, for those who reported using (+vitamin) or not using (–vitamin) vitamins at the time of admission

	+Vitamin, median (range); <i>n</i>	–Vitamin, median (range); <i>n</i>
GGT (IU/l)	99 (16–1959); <i>n</i> = 46	78 (13–1794); <i>n</i> = 54
ALT (IU/l)	42 (11–199); <i>n</i> = 43	35 (10–308); <i>n</i> = 51
AST (IU/l)	37.5 (15–195); <i>n</i> = 42	32.5 (13–300); <i>n</i> = 50
MCV (fl)	96.1 (84.6–108.1); <i>n</i> = 43	93.6 (74.1–112.2); <i>n</i> = 51
Bilirubin (mmol/l)	8 (3–52); <i>n</i> = 42	10 (4–34); <i>n</i> = 50
Albumin (mmol/l)	40 (20–47); <i>n</i> = 43	41 (29–55); <i>n</i> = 51
Magnesium (mmol/l)	0.83 (0.5–0.99); <i>n</i> = 29	0.84 (0.59–1.01); <i>n</i> = 37

Data are reported as median (range). Numbers of participants for each test are indicated as some data were missing for various reasons.

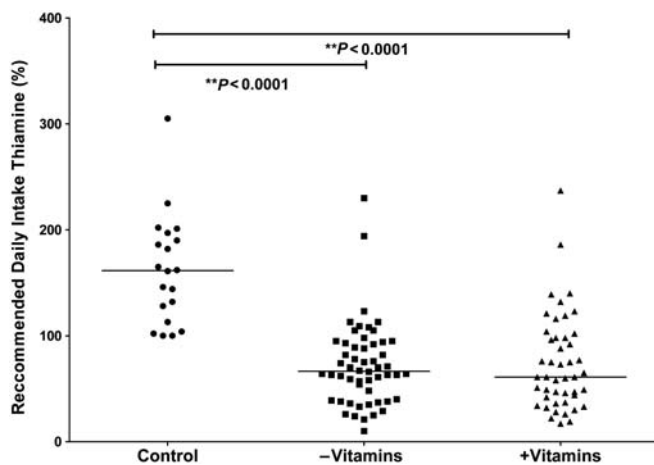


Fig. 2. The percentage of RDI of thiamine of alcohol-dependent participants relative to the control-group participants with no history of alcohol abuse. Black lines indicate the median value. The percentage of RDI estimated to be obtained from the diet is significantly greater for the control group than either group of alcohol-dependent participants ($P < 0.0001$).

DISCUSSION

At admission to inpatient treatment, blood thiamine levels of alcohol-dependent subjects who did not report taking vitamin supplements were significantly lower than blood thiamine levels in the control-group participants with no history of alcohol abuse or dependence, and were also lower than levels recorded in a previous study (Crowley and Gaughwin, 2011) of clients undergoing assessment for

fitness to hold a driver's licence (35% dependent). This suggests that, despite the mandatory addition of thiamine to wheat flour, people who are alcohol dependent remain at-risk for thiamine deficiency. Clients undergoing an assessment for fitness to hold a driver's licence are more likely to be employed than alcohol-dependent clients admitted for withdrawal (51% compared with 11%). Hence, socioeconomic status may also be a factor underlying the differing blood thiamine levels in these groups.

For the group of alcohol-dependent participants who reported use of vitamin supplements prior to admission to inpatient treatment, blood thiamine levels were not significantly different to the control-group levels suggesting that the regular use of vitamin supplements does help to reduce the risk of thiamine deficiency. The range of blood thiamine levels in the group reporting use of vitamin supplements was wide (Fig. 1). We did not ask about the frequency or the amount of supplement consumed and it seems likely that variability in consumption is a factor in the spread of blood thiamine levels in this group.

The estimated RDI of thiamine from the diet was significantly lower in both groups of alcohol-dependent participants compared with the control group (Fig. 2). At the same time no significant correlation was found between blood thiamine levels and reported alcohol consumption, albumin levels, MCV or GGT levels. The similar, and low, dietary thiamine intake in the two groups of alcohol-dependent participants supports a conclusion that poor dietary intake of thiamine is a factor in the low blood thiamine levels found in alcohol-dependent people and emphasises the importance of vitamin supplements in preventing thiamine deficiency in this group, particularly given an increased requirement for thiamine associated with alcohol withdrawal.

There was a significant correlation found between admission blood thiamine levels and bilirubin levels suggesting that severe liver disease may affect blood thiamine levels, but the small sample size, and particularly the small number of people with high bilirubin levels, reduces the strength of this finding.

The increase in blood thiamine levels from admission to discharge indicate that the thiamine supplementation regime, combining parenteral and oral administration that was used routinely in the inpatient unit, is effective. However, the thiamine reserves established during inpatient treatment would be quickly depleted following discharge with a relapse to heavy alcohol consumption and poor dietary habits. Hence it is recommended that the people who are alcohol dependent should be encouraged to take vitamin supplements on a

routine basis to help prevent thiamine deficiency. Administration of thiamine by parenteral and oral routes should be routine for alcohol-dependent people during withdrawal to respond to the increased need for thiamine at this time, particularly where there are reasons (e.g. low income, severe withdrawal) to suggest poor dietary intake of thiamine.

This study looks only at the levels of thiamine in the blood and suggests that poor diet associated with alcohol dependence may result in low blood thiamine levels while reported amounts of alcohol consumed were not an indicator of blood thiamine levels. The effect of alcohol consumption on cellular uptake of thiamine, including the transport of thiamine into the brain, and the utilization of thiamine in the body was not addressed by this study. An effect of alcohol on utilization of thiamine may result in an effective deficiency of thiamine even in the presence of adequate levels of thiamine in the blood. These aspects were beyond the scope of this study but are interesting questions for future research. Given that Australia is unique in mandatory fortification of bread and wheat flour with thiamine, a comparison across countries of thiamine levels and the prevalence of WKS in alcohol-dependent populations would also be of interest.

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