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Original article

Thiamine for preventing dementia development among patients with alcohol use disorder: A nationwide population-based cohort study

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SUMMARY

Objective of study: Alcohol use disorder is one of the most important factors contributing to dementia. This study examined the protective effect of thiamine administration on the incidence of dementia among patients with alcohol use disorder in Taiwan by evaluating a nationwide database.

Methods: We retrieved data for this retrospective cohort study from the Longitudinal Health Insurance Database 1995–2000. Patients receiving thiamine therapy after the diagnosis of alcohol use disorder were recruited as the thiamine therapy (TT) group, and the comparison group without TT (NTT group) included randomly assigned and age-, sex-, and index year-matched individuals with alcohol use disorder. Demographic data, comorbid medical disorders, and psychotropic medication use were evaluated and controlled. The cumulative defined daily dose (DDD) was analyzed to demonstrate the dose effect.

Results: Each group had 5059 patients. The TT group had a lower crude hazard ratio (0.76; 95% confidence interval: 0.60–0.96) of dementia than the NTT group. After adjusting for demographic data, comorbidity, and psychotropic medication use, the adjusted hazard ratio was 0.54 (95% confidence interval: 0.43–0.69). The significance existed among TT subjects with cumulative DDD higher than 23. The Kaplan–Meier analysis demonstrated a lower cumulative incidence of dementia in the TT group than in the NTT group.

Conclusion: The results indicated that thiamine therapy could be a protective factor for dementia development in patients with alcohol use disorder. Thiamine therapy should be a crucial part of the treatment plan and health policies to prevent dementia development or progression among patients with alcohol use disorder.

1. Introduction

The incidence of dementia increases with age, and it imposes a profound socioeconomic burden on caregivers and healthcare systems in Taiwan [1,2]. Sun reported that age-adjusted prevalence of all-cause dementia in individuals aged 65 years or older in 2011–2013 was 8.04% in Taiwan, and the incidence increased strongly with age, from 3.4% in people aged 65–69 years to 36.8% in those aged 90 years or older [3]. The prevalence of dementia in Taiwan is estimated to double every 20 years, reaching 0.32 million by 2030 and exceeding 0.6 million by 2050 [4]. This will place a heavy burden on Taiwan's health care system. The increasing longevity of the population is a major determinant of the “epidemic of dementia” in Taiwan and many countries. Taiwan's health policy makers must identify the risk factors and at-risk groups and develop appropriate management strategies.

1.1. Association between alcohol use disorder (AUD) and dementia

The impact of alcohol is extensive and includes behavioral and medical problems [5], deaths [5], and economic cost [6]. AUD was defined by fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5), ranging from use that puts patients at

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risk of health consequences to use causing multiple medical and/or behavioral problems [7]. Excessive alcohol use independently contributes to the development of dementia, and alcohol-related dementia was reported to be one of the most common types of dementia [8]. The overall proportion of alcohol-related early-onset dementia in three studies was approximately 10% [9,10]. Hypotheses to explain the etiology of alcohol-related dementia include ethanol-induced neurotoxicity and thiamine (vitamin B1) deficiency [11,12]. The neurotoxicity hypothesis suggests that the direct physiologic effects of chronic alcohol exposure can lead to structural and functional damage through glutamate excitotoxicity, oxidative stress, and disruption of neurogenesis [13].

Thiamine deficiency can lead to memory impairment [14]. Alcohol directly interferes with thiamine metabolism. Also, because of poor nutrition, alcohol users are at a higher risk of thiamine deficiency [15,16]. Thiamine deficiency is associated with structural changes such as volume changes in the mammillary bodies, a key area of the brain concerning memory [17]. It can result in the most severe form of cognitive Wernicke–Korsakoff syndrome, characterized by the clinical triad of oculomotor abnormalities, cerebellar dysfunction, and altered mental states caused by neuronal loss, hemorrhagic lesions, and profound memory impairment [14]. In addition, thiamine deficiency may be associated with dementia as thiamine-dependent enzymes are critical components of glucose metabolism in the human brain [18]. In preclinical models, reduced thiamine intake can give rise to Alzheimer disease-like abnormalities, including memory deficits, plaques, and hyperphosphorylation of tau. Many studies have shown that thiamine deficiency is associated with neurological complications, including cognitive deficit and encephalopathy [18]. Thus, thiamine deficiency could be an important factor contributing to dementia, especially among patients with AUD [18].

1.2. Thiamine supplementation in AUD

Many studies have established the importance of TT in Wernicke–Korsakoff syndrome [19]. However, few have discussed the therapeutic effect of thiamine in AUD or alcohol-related dementia. Alcohol use being the most common etiology of Wernicke–Korsakoff syndrome in modern society [16], we hypothesized that the thiamine supplementation could prevent patients with AUD from developing dementia. Thus, this study retrospectively evaluated the hazard ratio of dementia among patients with AUD with TT versus those without TT based on a survival analysis in a nationwide population-based cohort database in Taiwan. This is the first study to discuss the therapeutic effect of TT on dementia development in patients with AUD.

2. Methods

2.1. Data source

We retrieved data on study subjects for this cohort study from the Longitudinal Health Insurance Database 2000 (LHID2000). The LHID2000 consists of claims data from 1,000,000 individuals; it was implemented in 1995 to provide comprehensive and easily accessible medical care for all residents in Taiwan. Some independent researchers have demonstrated the high validity of data derived from the Taiwanese NHI program. The LHID2000 enables researchers in Taiwan to trace the medical services of these selected 1,000,000 individuals from the beginning of the Taiwan NHI program [20]. All clinical diagnoses were recorded using codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). For privacy and security reasons, all identifiable patient data are scrambled cryptographically by the NHIRD before being released for research [21]. The Institutional Review Board of Kaohsiung Medical University Hospital approved this study (KMUHIRB-(I)-20170170).

2.2. Study population

In this study, we conducted a retrospective cohort study of patients aged 40 years and older with newly diagnosed AUD (ICD-9-CM codes: 303, 305.0, and V11.3), but without a previous diagnosis of dementia or alcohol-induced persisting amnestic disorder (ICD-9-CM codes 290.0–290.4, 291.1–291.2, 294.1331.0–331.2, and 331.82) during 2000–2009. Patients were grouped into the TT group (n = 5059) if they received TT after AUD diagnosis or a randomly-assigned comparison cohort called the non-thiamine therapy group (NTT group; n = 5059) who were matched to thiamine users by age, sex, and index year using propensity score matching. We did not include patients aged less than 40 years because of the low prevalence of dementia in that age group; we excluded patients with missing information on age or sex as well as those diagnosed with dementia before the index date.

2.3. Exposure to thiamine

Drug usage information was obtained from the outpatient prescription database; the information included drug dosage, date of prescription, usage days, and total number of pills. To investigate the effect of dose, the cumulative use of thiamine (ATC code A11DA01) was calculated as cumulative defined daily dose (DDD). In this study, we divided thiamine cumulative DDDs into quartiles: low dose (<23 DDDs), moderate dose (23–121 DDDs), and high dose (>121 DDDs).

2.4. Diagnosis of dementia

All patients were followed up until they were diagnosed with dementia (ICD-9-CM codes 290.0–290.4, 291.1–291.2, 294.1, 331.0–331.2, and 331.82), were censored for failure to follow-up, withdrew from the NHI, or until December 31, 2013.

2.5. Potential confounders

We defined users of each medication during 120 days before index date. We divided insurance range into three groups based on monthly income: low income (<20,000 New Taiwan Dollar [NTD]), median income (20,000–39,999 NTD), and high income (≥40,000 NTD). Inpatient and outpatient files from the year prior to the index date were used to obtain information on comorbidities, including diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), hypertension (ICD-9-CM codes 401–405), coronary artery disease (CAD; ICD-9-CM codes 410–414), heart failure (HF, ICD-9-CM code 428), stroke (ICD-9-CM codes 430–438), head injury (ICD-9-CM codes 801–804, 850–854, and 959.01), chronic liver disease and cirrhosis (ICD-9-CM code 571), rheumatoid arthritis (ICD-9-CM code 714), chronic kidney disease (ICD-9-CM code 585), chronic obstructive pulmonary disease (ICD-9-CM codes 490–492, 494, and 496), and tobacco abuse/dependence (ICD-9-CM code 305.1) before the index date [22,23]. Among patients with AUD, we also considered other potential confounding factors including antidepressant agents therapy and benzodiazepine. We defined users of each medication for the 120 days before index date.

2.6. Statistical analysis

Either Pearson's chi-squared test or Fisher's exact test was used to compare each categorical variable; categorical variables included

Table 1
The demographic data, comorbidities, and Medication of the analyzed sample (N = 10,108).

	VIT-B1 user (−) (n = 5054)	VIT-B1 user (+) (n = 5054)	p value
	N (%)	N (%)	
Age, mean ± SD	53.13 (10.18)	53.41 (10.25)	0.173
40-64	4255 (84.2)	4197 (83.0)	0.202
65-74	602 (11.9)	655 (13.0)	
>=75	197 (3.9)	202 (4.0)	
Gender			
Female	705 (13.9)	699 (13.8)	0.863
Male	4349 (86.1)	4355 (86.2)	
Insurance range			
<NT 20,000	2615 (51.7)	2578 (51.0)	<0.001
NT20,000 − NT 39,999	1681 (33.3)	1948 (38.5)	
>NT 40,000	758 (15.0)	528 (10.4)	
Comorbidities			
Diabetes	880 (17.4)	1102 (21.8)	<0.001
Hyperlipidemia	1404 (27.8)	1789 (35.4)	<0.001
Hypertension	1804 (35.7)	2173 (43.0)	<0.001
Coronary artery disease	217 (4.3)	312 (6.2)	<0.001
Heart failure	53 (1.0)	71 (1.4)	0.104
Stroke	244 (4.8)	280 (5.5)	0.106
Head injury	368 (7.3)	514 (10.2)	<0.001
Chronic liver disease and cirrhosis	1272 (25.2)	1878 (37.2)	<0.001
Rheumatoid arthritis	172 (3.4)	284 (5.6)	<0.001
Chronic kidney disease	361 (7.1)	544 (10.8)	<0.001
Chronic obstructive pulmonary disease	1638 (32.4)	2060 (40.8)	<0.001
Tobacco abuse/dependence	3180 (62.9)	2544 (50.3)	<0.001
Medication			
Antidepressant agents	168 (3.3)	283 (5.6)	<0.001
Benzodiazepine	851 (16.8)	1557 (30.8)	<0.001

age strata, sex, insurance range, disease history, and medication. Independent t-testing was used to compare continuous variables. We calculated the incidence density rate of dementia (person-years) for each subgroup and conducted univariate and multivariate Cox proportional hazard regression analyses to calculate the hazard ratios and 95% confidence intervals (CIs) of the risk of dementia. The multivariate models were adjusted for age, monthly income, and comorbidities. A Kaplan–Meier curve was used to assess the cumulative incidence of dementia between the two cohorts, and the log-rank test to test the differences between the thiamine cohort and the comparison cohort. All statistical analyses were performed using SAS (SAS System for Windows, v. 8.2, SAS Institute, Cary, NC, USA). We used the conventional threshold of $p \leq 0.05$ to assess statistical significance.

3. Results

There was no difference in age and sex between the TT and NTT groups in AUD as they had been matched in this study (Table 1). A higher proportion of the NTT group was classified in the high insurance range. Further, the TT group was more likely than the NTT group to have comorbidities with diabetes, hyperlipidemia, hypertension, coronary artery disease, heart failure, stroke, head injury, chronic liver disease and cirrhosis, rheumatoid arthritis, chronic kidney disease, chronic obstructive pulmonary disease, or tobacco abuse/dependence. In general, this result demonstrated that the TT group had a higher rate of comorbidities that could contribute to the risk of dementia. Relative to the NTT group, a higher proportion of the TT group had ever taken antidepressants and benzodiazepines.

From 2000 to 2009, 130 (2.57%) patients in the TT group and 163 (3.23%) in the NTT group developed dementia. The Kaplan–Meier analysis of the cumulative incidence of dementia demonstrated it to be significantly lower for the TT group than for the NTT group (log-rank test, $p < 0.001$; Fig. 1). The incidence density rate of dementia was lower in the TT group than in the NTT group. The risk of dementia was significantly lower for patients in the TT group than for those without TT after adjusting for sex, age, and comorbidities (adjusted hazard ratio = 0.54, 95% CI = 0.43–0.69; Table 2). Analysis stratified by cumulative DDDs demonstrated that the TT group had a significantly lower hazard ratio when the cumulative DDD value was ≥23 (Table 2). There was no difference in the hazard ratio between the TT and NTT groups when the cumulative DDD value was <23.

We further evaluated the hazard ratio of the TT group versus the NTT group by stratifying based on the risk factors of dementia. The TT group had a lower hazard ratio in different age groups, in both sexes. They also had a lower hazard ratio than the NTT group irrespective of the presence of diabetes, hyperlipidemia, hypertension, coronary artery disease, stroke, head injury, chronic liver disease and cirrhosis, chronic kidney disease, chronic obstructive pulmonary disease, tobacco abuse/dependence, and benzodiazepine use. However, no difference was found in hazard ratios between the two groups among those who were high in insurance range, rheumatoid arthritis, heart failure, and antidepressant use, possibly because of the inadequate number of patients in this subgroup.

4. Discussion

The wide impact of dementia has already been discussed in recent years and has become a major component of health policies in Taiwan and other countries. The World Health Organization estimated that 47 million cases of dementia existed worldwide in 2015 and predicted that this will triple by 2050 owing to the aging of the population [24]. There is no cure, and nor are there prevention studies to identify modifiable risk factors and protective factors to delay the onset or reduce the risk of dementia [25]. In AUD with Wernicke–Korsakoff syndrome, considerable research

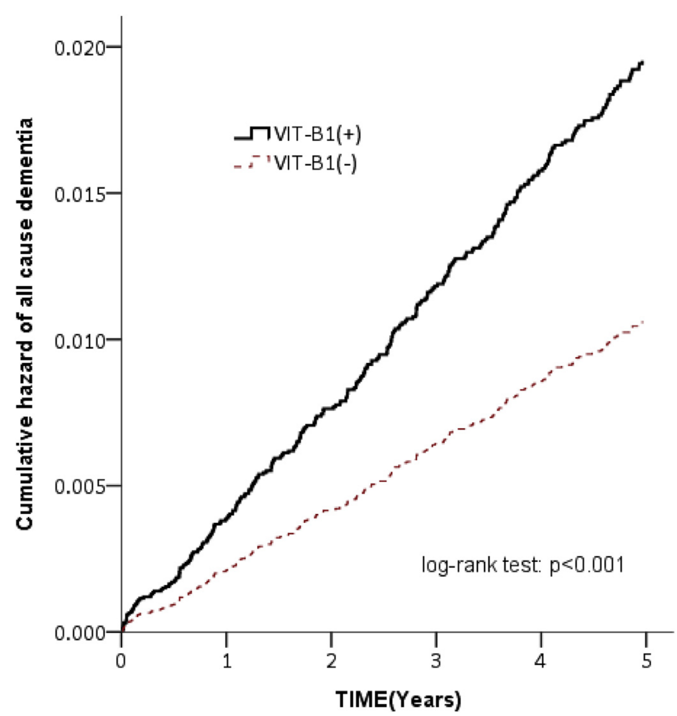

Fig. 1. Kaplan–Meier analysis of the cumulative incidence of dementia.

Table 2
Risk of all-cause dementia associated with thiamine use in patients with alcohol use disorder (N = 10,108).

	Case no	Per 1000 person year	Crude hazard ratio (95% CI)	p value	Adjusted hazard ratio (95% CI)	p value
VIT-B1 user (−)	163	7.45	Ref.		Ref.	
VIT-B1 user (+)	130	5.65	0.76 (0.60–0.96)	0.019	0.54 (0.43–0.69)	<0.001
Cumulative DDDs						
<23	45	5.90	0.79 (0.57–1.10)	0.166	0.80 (0.58–1.12)	0.199
23–121	41	5.35	0.72 (0.51–1.01)	0.058	0.53 (0.37–0.75)	<0.001
>121	44	5.69	0.77 (0.55–1.07)	0.116	0.40 (0.28–0.57)	<0.001

Adjusted for age, insurance range, and comorbidities.

has focused on the protective role of thiamine supplementation. This syndrome is often complicated by alcoholism because alcohol reduces thiamine absorption [18]. The gold standard of treatment for Wernicke–Korsakoff syndrome is thiamine supplementation according toTaiwan's health insurance system, and such treatment is always recorded in the database. However, excessive alcohol use contributes to dementia other than Wernicke–Korsakoff syndrome [23].

This is the first study to discover that in addition to benefitting patients with Wernicke–Korsakoff syndrome, thiamine supplementation could also be a protective factor against dementia in AUD. We found that the TT group had significant proportions of comorbidities, including endocrine diseases (diabetes and hyperlipidemia), cardiovascular diseases (hypertension, coronary artery disease, and heart failure), neurological diseases (head injury), gastrointestinal diseases (chronic liver disease and cirrhosis), respiratory diseases (chronic obstructive pulmonary disease), and psychotropic medication use (antidepressant, benzodiazepine, and tobacco abuse). The TT group had a lower crude hazard ratio of dementia than the NTT group had. After adjusting for these diseases, the TT group had less chance of developing dementia. The results indicated that the protective effect of thiamine was independent of the effect of medical comorbidity and psychotropic medication use.

Thiamine deficiency has been linked to impaired cognition for decades. First, brain glucose metabolism requires thiamine at critical regulatory steps [26]. Glucose metabolism in the brain is unique and much higher than in other body tissues. The brain represents only 2% of body mass but uses 20% of the glucose. The high rate of metabolism may account for the brain's sensitivity to thiamine deficiency. Glucose metabolism is diminished by 20%–30% in temporal and frontal regions of patients with thiamine deficiency, which can be improved by the administration of thiamine [18]. Second, neurochemical studies in animal models have revealed that thiamine deficiency could be an important component of Alzheimer dementia pathophysiology, including memory deficits, plaques, and hyperphosphorylation of tau [27,28]. Third, thiamine deficiency is also linked to neurotransmitter dysregulation. Thiamine deficiency produces a central cholinergic deficit [29] and induces excess glutamate release [30,31]. These two pathways are important targets of Alzheimer's disease medications: N-methyl-D-aspartate (NMDA) antagonists (e.g., memantine) and acetylcholinesterase inhibitors (e.g., donepezil). Chronic, long-term thiamine insufficiency may represent an upstream noxious event that later leads to the formation of neuritic plaques [32] and neurofibrillary tangles [27,28]. Thiamine also has many other roles such as binding to amyloid and prions [33], altering acetylcholine release [34], and acting as an antioxidant [35].

Alcohol reduces thiamine absorption and leads to thiamine deficiency [18]. In the present study, patients who received thiamine supplementation showed a lower chance of developing dementia, perhaps because thiamine balances the neurotransmitter transmission and decreases the formation of Alzheimer dementia pathophysiology such as plaques and tau protein.

Furthermore, thiamine deficiency produces selective cell death in the brain [36,37], with the submedial thalamic nucleus being one of the most sensitive regions. Brain imaging data of Wernicke–Korsakoff syndrome also revealed abnormal shrinkage over multiple important brain areas such as the frontal lobe, mammillary bodies, and thalamus [38]. Administration of thiamine could reverse the effects of thiamine deficiency on thiamine-dependent enzymes, behavior, and neuronal death before the changes are irreversible [32].

4.1. Clinical implications

Based on our results, all medical staff managing AUD should educate the patients on thiamine supplementation and ensure that adequate thiamine nutrition is included in the medical treatment plan and health policy. Thiamine is cheap, efficient, and easily available. Developing a therapeutic strategy of adequate thiamine supplementation could retard dementia development or progression, and thiamine should be given as early as possible in patients with AUD.

Thiamine deficiency is involved in the etiology of dementia through not only alcohol use but also other mechanisms, such as glutamate pathway. Thiamine has been reported to improve cognition in an animal study [39]. Thus, the protective effect of thiamine supplementation on dementia in subjects without AUD should be evaluated in the future.

The major strength of this study is the use of nationwide population-based database and the longitudinal, observational design with a long follow-up period; the large sample size provided sufficient statistical power to explore the relationship between AUD and dementia with and without TT. However, there are certain limitations. First, we included only patients with newly diagnosed dementia and AUD seeking medical help during the study period, which may not be fully representative of the general TT population. Thus, the risk of developing dementia in patients with AUD may have been underestimated. Second, information on potential confounders such as education year, body weight and body mass index, biological data such as imaging reports, and blood examination data was not available in the NHIRD. Third, AUD and dementia diagnoses were based on diagnostic codes, which were entered by clinical physicians into the NHIRD database, rather than verified through standardized interviews with patients.

In summary, TT attenuated the risk of developing dementia in patients with AUD. TT is cheap and easily available, and should be included in health policies for AUD; adequate thiamine nutrition would be helpful to patients with AUD. Future studies should measure the precise, optimal dosage of thiamine.

Conflict of interest

None.

Acknowledgments

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