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Critical review

Relationship of alcohol intake and thiamine deficiency in heart failure

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Abstract

Introduction

The purpose of this paper is to summarize the relationship of alcohol intake with thiamine deficiency and with heart failure and the manner in which they interact with each other.

Discussion

Moderate alcohol consumption has shown to decrease cardiovascular mortality. However, heavy alcohol consumption is associated with alcoholic cardiomyopathy. Excessive alcohol intake is associated with thiamine deficiency. Moreover, heart failure is also related to thiamine deficiency, and thiamine supplementation has shown to increase left ventricular ejection fraction.

Conclusion

Thiamine deficiency should be further studied in heart failure, and more research is needed to show the effect of thiamine supplementation in heart failure.

Introduction

Excessive alcohol use is the third leading lifestyle-related cause of death for people in the United States each year, placed behind tobacco and improper diet/lack of physical activity, which are the first and second lifestyle-related causes of death, respectively[1].

Alcohol in alcoholic drinks is mainly ethanol. The ethanol molecule can, because of its structure and small size, diffuse readily across

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cell membranes. Because there is no identifiable receptor, the mode of action is non-specific. The effects of ethanol are complex and contain one or several of the following mechanisms: (1) changes in membrane fluidity, (2) changes in the relative concentration or organization of specific membrane lipids, (3) alterations in specific protein domains (that in turn alter membrane protein function), (4) stimulation or attenuation of membrane signal transduction cascades and related intra-cellular enzyme systems (e.g. protein kinase A and C), (5) changes in channel function, (6) changes in receptor number and subunit expression and finally (7) modulation of neurotransmitters and neuromodulator systems[2].

However, besides these rather detrimental effects, it has extensively been shown that in apparently healthy subjects, moderate alcohol consumption (1–2 drinks/day) decreases cardiovascular and all-cause mortality[3]. Also, the risk of coronary heart disease, ischaemic strokes and amputations due to peripheral vascular disease is decreased with moderate alcohol consumption[4]. Mechanisms supporting this positive effect of moderate alcohol consumption include beneficial regulation of lipids and fibrinolysis, decreased platelet aggregation and coagulation factors and beneficial effects on endothelial function, inflammation and insulin resistance[3].

The relationship between alcohol and total mortality appears to be J-shaped[5]. Consequently, it has been a matter of great debate on what amount and duration of alcohol abuse is required to produce detrimental effects. It appears that

most alcoholic patients with detectable changes in cardiac structure and function report consuming >90 g alcohol per day for ≥5 years. Therefore, heavy drinking refers to more than six standard alcoholic drinks per day for more than 5 years.

Excessive alcohol intake is also related to thiamine deficiency. Thiamine deficiency, especially in relation to alcohol abuse, leads to Wernicke encephalopathy and Korsakoff syndrome[6]. Thiamine deficiency can also result in wet beriberi. Clinical features of wet beriberi will respond within hours to a bolus of thiamine[7]. There is increasing evidence that thiamine deficiency also plays a role in heart failure.

The purpose of this paper is to summarize the relationship of alcohol intake with thiamine deficiency and with heart failure and the way they interact with each other.

Discussion

Alcohol and heart failure

Lifestyle modification including moderation of alcohol intake is important in cardiovascular disease. Among heart failure patients, one in five patients drink two or more alcoholic beverages everyday[8]. This puts them at risk of alcohol dependence.

The acute effects of alcohol consumption are mainly obtained from isolated and whole animal heart preparations and young healthy human persons[2]. Results of these studies are not clear, and the main limitation is that the sample sizes range from 4 to 12.

Greenberg et al.[9] specifically researched the acute effects of alcohol consumption on haemodynamic and echocardiographic parameters in

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eight heart failure patients. Alcohol ingestion resulted in rather favourable haemodynamic effects, which include a significant reduction in mean arterial pressure, pulmonary capillary wedge pressure and systemic vascular resistance.

There is limited data on the long-term effects of moderate alcohol intake in heart failure patients. Cooper et al.[10] specifically investigated the effects of moderate drinking in heart failure patients. It was shown that moderate drinking is associated with a significant reduction in relative risk for all-cause mortality and fatal myocardial infarction in the group with ischaemic left ventricular dysfunction. However, in the non-ischaemic left ventricular dysfunction group, moderate drinking had no effect on any of the outcome parameters.

In a meta-analysis on alcohol consumption and mortality in patients with cardiovascular disease (coronary heart disease, acute myocardial infarction and stroke), it was shown that there was a J-shaped relationship between alcohol consumption and all-cause and cardiovascular mortality[3]. It seems that the effect of moderate drinking is similar in patients with cardiovascular disease as in healthy subjects.

As moderate alcohol consumption appears to be safe and may also have beneficial effects, one could argue that moderate drinking should be recommended. However, there is currently insufficient evidence to recommend the use of alcohol in heart failure patients that do not currently consume drink alcohol. One reason to be conservative is that there is considerable individual variation in the effect of alcohol consumption. There is a three- to four-fold variation in the rate of alcohol metabolism between individuals, and there is a two- to three-fold variation in the pharmacodynamics of alcohol due to individual differences[11].

Long-term heavy alcohol consumption is known to lead to non-ischaemic dilated cardiomyopathy, which is referred to as alcoholic cardiomyopathy if heavy drinking is reported. Alcoholic cardiomyopathy is responsible for 21%–36% of all cases of non-ischaemic dilated cardiomyopathy in Western Society. The prevalence of alcoholic cardiomyopathy among alcoholics is variable and ranges from 23% to 40%[11]. It occurs more in men than women, although women are more sensitive to the toxic dose of alcohol. Limited data are available on the amount and duration of consumption required to produce symptomatic alcoholic cardiomyopathy. However, in general, heavy drinking (>90 g alcohol per day, which equals six standard alcoholic drinks per day) for more than 5 years puts patients at risk for the development of asymptomatic alcoholic cardiomyopathy[2].

Clinical findings in patients with alcoholic cardiomyopathy are identical to idiopathic cardiomyopathy, with dilatation and impaired contraction of the left or both ventricles, increased left ventricular end-diastolic volume, increased left ventricular mass and a left ventricular ejection fraction below 45%[12]. Therefore, the diagnosis of alcoholic cardiomyopathy is based on the coincidence of heavy alcohol consumption and a global myocardial dysfunction with no other underlying myocardial disease. However, alcoholic cardiomyopathy is not necessarily associated with deterioration after ceasing alcohol consumption while the idiopathic form is[12]. If patients with alcoholic cardiomyopathy do not abstain from alcohol, they have a poorer prognosis and significantly higher mortality rates compared with those who do abstain. The 4-year mortality can be as high as 50%[2,13].

Alcohol and thiamine
Alcohol consumption leads to thiamine deficiency by decreasing the transport of thiamine across the intestinal mucosa, impairing capacity of the liver to store thiamine and impairing the phosphorylation of thiamine to the more biological active thiamine diphosphate[14].

The active form of thiamine, thiamine diphosphate, is the co-enzyme of three major enzymes: transketolase (TK), pyruvate dehydrogenase complex (PDH) and α-ketoglutarate dehydrogenase (α-KHD). These enzymes are present in the mitochondria and are essential in citric acid cycle and for the generation of ATP. Alcohol especially decreases the amount of thiamine diphosphate. *In vitro* and *in vivo* experiments have shown that thiamine pyrophosphokinase is inhibited by ethanol[15]. Furthermore, chronic ethanol intake leads to increased thiamine diphosphatase[16]. As shown in Figure 1, this double action, due to chronic exposure to ethanol, further decreases the amount of thiamine diphosphate.

Moreover, the metabolism of alcohol raises the demand for thiamine. In this way, alcohol-dependent people require more thiamine than non-alcoholic people. Other contributing factors to thiamine deficiency in alcoholics are self-neglect and low content of vitamins and minerals of alcoholic beverages.

Thiamine deficiency in heart failure patients
Thiamine deficiency is commonly linked to alcoholism, but can be seen in other patients as well. Special attention is paid in this respect to people with a staple diet of white bread or polished rice[17,18]. But, even more recently, thiamine deficiency has been described in several populations that rely entirely on the provision of nutrition by outside sources[19,20]. Also, parenteral nutrition can be thiamine-deficient, which can cause an outbreak of thiamine deficiency in infants[21].

Thiamine deficiency can lead to wet beriberi. The infantile form is well described in infants who were fed parenteral nutrition that
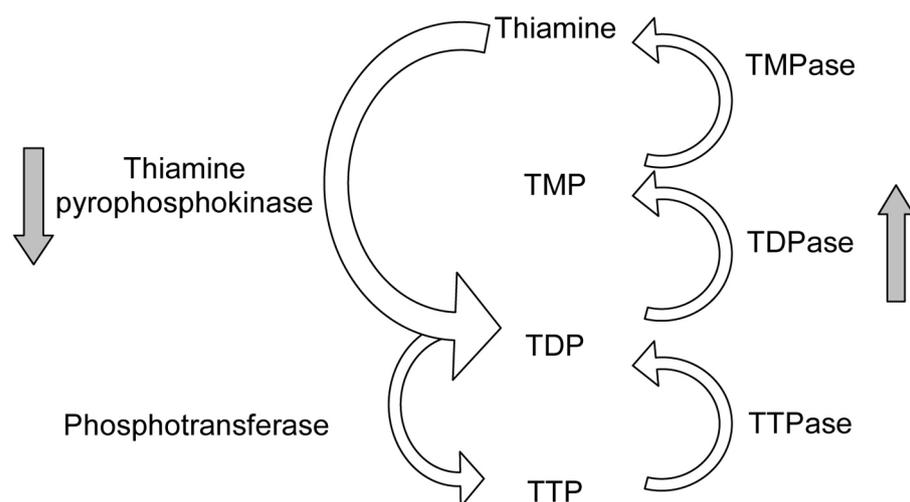
Figure 1: Thiamine phosphorylation and dephosphorylation. Influence of alcohol is represented with *grey arrows*, resulting in decreased thiamine diphosphate (TDP).

appeared to be thiamine-deficient[21]. Symptoms in adults can be divided into a common high output state and an uncommon low output state. Symptoms of wet beriberi in infants and adults are summarized in Table 1.

Among patients with heart failure, thiamine deficiency is highly prevalent. Potential contributing factors of thiamine deficiency in patients with heart failure are loop diuretic use, malnutrition, advanced age, heart failure severity and frequent hospitalization. Incidence of thiamine deficiency in heart failure patients has been reported to be 33%, whereas thiamine deficiency was present in 12% of the control subjects[22]. In this study by Hanninen et al., thiamine deficiency was related to urine thiamine loss, absence of intake of thiamine-containing supplements and preserved renal function.

Furosemide treatment has shown to exacerbate the thiamine deficiency, probably by preventing the reabsorption of thiamine and thereby increasing the urinary excretion of thiamine[23]. Digoxin has been shown to have a similar effect, and furosemide and digoxin have an additive effect if used simultaneously[24].

By Zenuk et al.[25] it was shown that with furosemide therapy, at doses higher than 80 mg/day, prevalence of thiamine deficiency was 98%. However, thiamine deficiency may also occur with long-term use of smaller dosages of diuretics.

In vitro experiments showed that thiamine supplementation has a cytoprotective effect on cardiomyocytes during hypoxic insult[26]. Hypoxia is an important cause of cell death in myocardial infarction, cardiomyopathy and chronic heart failure. It has also been shown that the cardiac contractility is reduced by thiamine deficiency[27].

Until now, four studies examined the effect of thiamine supplementation on cardiac function in heart failure patients[28–31]. Three of these studies, of which two were randomized, found an improvement of left ventricular function after thiamine supplementation[28–30]. One study did not show a significant effect of thiamine on the clinical course of cardiomyopathy, but cardiac function was not assessed by echocardiography[31]. The most recent study was a randomized, double-blind, placebo-controlled, crossover pilot study in nine patients[28]. After 28 days of treatment with 300 mg thiamine a day, the left ventricular ejection fraction was significantly increased.

Table 1 Clinical co-features of thiamine deficiency related to different forms of beriberi	
Infantile beriberi	
Cardiomyopathy	
Aphonia	
Absent deep-tendon reflexes	
Vomiting	
Diarrhoea	
Weight loss	
Restlessness	
Nystagmus	
Ophthalmoplegia	
Respiratory symptoms	
Wet beriberi	
Common high output state	*Uncommon low output state*
Heart failure	Severe hypotension
Orthopnea	Lactic acidosis
Pulmonary oedema	Absence of oedema
Peripheral oedema	

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In a small observational study, it was shown that thiamine levels decreased during coronary artery bypass graft. The investigators propose that increased metabolic demand will increase the usage of thiamine in "stress situations" and will lead to increased depletion.

Interaction between alcohol, thiamine deficiency and heart failure

In Figure 2, the schematic relationship of alcohol, thiamine deficiency and heart failure is depicted. Whereas moderate alcohol intake seems to decrease cardiovascular and all-cause mortality, prolonged alcohol abuse results in alcoholic cardiomyopathy. Furthermore, alcohol is directly toxic to the cardiomyocyte. Therefore, alcohol abuse will lead to heart failure. Alcohol abuse also results in thiamine deficiency by improper intake of thiamine through self-neglect, decreased thiamine diphosphate, as a direct effect of alcohol and raised demand for thiamine.

Also, heart failure and thiamine deficiency interplay together. Heart failure patients are prone to thiamine deficiency by their general health factors (such as malnutrition and advanced age), and also treatment with furosemide and digoxin has

shown to increase thiamine deficiency. Thiamine deficiency was shown to decrease the left ventricular ejection fraction, thereby requiring more intensive treatment and probably worsening of the thiamine deficiency.

Conclusion

Heart failure and thiamine deficiency are closely linked not only because of the effect of alcohol on both of them but also because of their interplay together. Therefore, thiamine deficiency should be further studied in heart failure, and more research is needed to show the effect of thiamine supplementation in heart failure.

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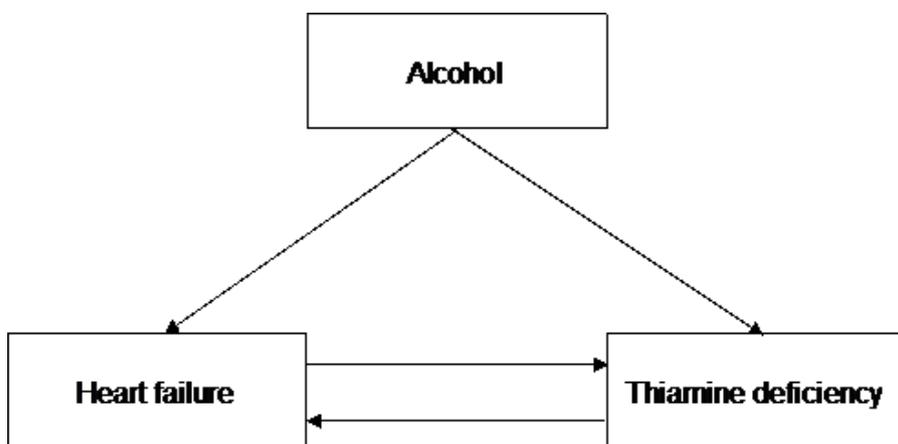
Figure 2: Schematic relationship of alcohol, thiamine deficiency and heart failure.

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