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Research Article

The acute effect of thiamine on serum insulin levels and some biochemical parameters in excessive alcohol-consuming rats

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ABSTRACT

In the present study, it was aimed to investigate the effectiveness of thiamine in rats with a binge drinking model. For this purpose, a total of 21 Sprague Dawley rats were divided into three equal groups; control, alcohol, and thiamine+alcohol groups. The thiamine+ alcohol group was given thiamine at a daily dose of 100 mg/kg by oral gavage, starting 2 days before the alcohol administration. Alcohol and thiamine+alcohol groups were given 3.45g/kg/day alcohol as 20% for 3 consecutive days. At the end of the study, while serum total bile acid, total bilirubin, and insulin levels increased in rats in the alcohol group compared to the rats in the control group; total protein and albumin levels decreased ($p<0.05$). In the thiamine + alcohol group, LDL-cholesterol, total cholesterol, bile acid levels, and AST enzyme activity increased, while ALT enzyme activity and total protein levels decreased compared to the control group ($p<0.05$). There was no statistically significant result in the values in the thiamine + alcohol group compared to the alcohol group. It might be concluded that acutely administered thiamine supplementation had no effect on alcohol-induced biochemical parameter changes in binge drinking animals. In this positive effect, studies with longer-term thiamine use may be needed.

INTRODUCTION

It is reported that excessive alcohol consumption, which is among the highest risk factors for mortality, is an important predisposing agent for more than 200 diseases (O'Keefe et al, 2014). Although most of the studies focused on chronic alcohol consumption, the most common type of drinking especially in the young population is excessive alcohol consumption (Ngandeu et al, 2018). Excessive alcohol consumption is a concern especially in young individuals, particularly due to neurotoxic effects (Bajac et al 2016). Binge drinking, is a type of excessive alcohol consumption; has been defined as the consumption of five or more units of alcoholic beverage in a period of approximately two hours (Wechsler et al, 1994). Binge (excessive) drinking is considered a public health problem associated with metabolic diseases such as diabetes and obesity. In addition, the influence of binge drinking on glucose metabolism has not yet been fully elucidated (Naimi et al 2003).

The effects of alcohol on glucose metabolism and insulin secretion have been variously reported, depending on the amount of alcohol consumed, type of meal, and duration of drinking. Alcohol is metabolized in the body to acetaldehyde and acetic acid, and these metabolites and reactive oxygen species formed in the metabolic process can directly affect glucose metabolism. It is thought that the mechanism by which excessive drinking causes hyperglycemia is that alcohol directly inhibits glucose-stimulated insulin secretion and inhibits glycogen synthesis in the liver, preventing glucose utilization by oxidative and non-oxidative pathways. Also, although alcohol does not inhibit the binding of insulin itself, it can cause insulin resistance by causing abnormalities in intracellular signalling after insulin binds to insulin receptors in peripheral tissues. On the other hand, an increase in insulin secretion is also observed due to the intracellular signalling effect of alcohol (Jang and Eun, 2012).

Thiamine (Vitamin B1) is a necessary vitamin for all tissues for the continuity of the activities of different enzymes involved in the metabolism of carbohydrates. Thiamine is converted to thiamine pyrophosphate (the active form of thiamine) by the enzyme thiamine diphosphokinase in the liver (Bettendorff et al., 1996). Conversion of thiamine to its active form is decreased, especially in liver damage as a result of chronic alcohol consumption. In cases of thiamine deficiency, disorders occur in the pathways in the synthesis of nucleic acids, fatty acids, etc. in the body because thiamine is needed for the functions of various enzymes necessary for the metabolism of cells (Chandrakumar et al. 2018). Three of these enzymes; the alpha-keto glutamate dehydrogenase, the pyruvate dehydrogenase complexes and transketolase play important roles in glucose and lipid metabolism. Alcohol damages the intestinal lining, causing disrupted thiamine absorption from the gut. Therefore, a deficiency of thiamine may be seen in the use of alcohol (Gastaldi et al. 1989). In addition, thiamine needs to

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be transformed into an active form in order to act as a cofactor of enzymes involved in lipid and glucose metabolism. The enzyme thiamine pyrophosphpkinase converts thiamine to thiamine pyrophosphate (the active form of thiamine). In excessive alcohol intake, this enzyme activity is impaired, therefore, there is a decrease in thiamine activity (Langlais, 1995). As a result of the above-mentioned mechanisms, it has been revealed that alcohol use can be caused thiamine deficiency and, as a result, deterioration in metabolic pathways.

This study was aimed to investigate the effect of thiamine supplementation on changes of some serum biochemical parameters levels and serum insulin hormone levels of high alcohol intake 1-2 times a month, which is very common in young population.

MATERIAL and METHODS

This study was carried out in Mehmet Akif Ersoy University's experimental animal breeding and experimental research center. (Ethical approval no: 688/2020)

Animals

Totally 21 adult female Spraque Dawley rats were used in the study. During the study, 7 rats were housed in each cage. Rats in plastic rat cages, at 23±2 °C of room temperature, in a 50±10% relative humidity environment, in a 12 h light/12 h dark cycle were fed ad-libitum. At the end of the one-week adaptation period, the rats were divided into three equal groups as control, alcohol, and thiamine+alcohol groups. The rats were given standard rat food and regular tap water ad libitum during the experiment. The thiamine+alcohol group was given thiamine hydrochloride (Sigma Aldrich, Germany) at a daily dose of 100 mg/kg by oral gavage, starting 2 days before the alcohol administration. Alcohol and thiamine+alcohol groups were given 3.45 g/kg/day of ethanol intraperitoneally. Ethanol administration to both groups continued for 3 days, and thiamine was continued to be given to the thiamine+alcohol group these days. In the control group, saline was administered intraperitoneally on the days given alcohol. At the end of the 5th day, blood samples were collected from the animals for biochemical analysis, and euthanasia procedures were performed.

Collection of Samples

At the end of the experiment, all rats in the study were collected blood by cardiac puncture under general anesthesia (thiopental anesthesia, 40 mg/kg) and the rats were sacrificed by cervical dislocation. Blood samples were centrifuged at 3000 rpm for 15 minutes for obtaining serum samples. Serum samples were stored at -20 °C until the analysis.

Biochemical Analysis

The analysis of biochemical parameters (Glucose, triglycerides, total-cholesterol (C), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bile acid, total protein, total bilirubin, albumin) of blood serum samples were done with an autoanalyzer (Randox-Monaco, England) and were carried out with the spectrophotometric measurement method.

Serum Insulin Hormone Analysis

Insulin hormone levels in blood serum samples were measured with a microplate reader (Biotek-Epoch, USA) at 450 nm wavelength using the ELISA method using a commercial kit (BT-Lab, China) according to kit procedures.

Statistical Analysis

Firstly, a normality test was applied to determine whether the data were parametric or nonparametric. Since the number of data in each group was <30, the results were interpreted according to the Shapiro-Wishlk test in the normality test. In this case; since $p>0.05$ for glucose, triglycerides, total cholesterol (C), HDL-C, ALT, AST, bile acid, total protein, albumin, and insulin variables, these variables show normal distribution within the three groups. Since $p<0.05$ in the thiamine group for the LDL-C variable, the thiamine group for the ALP variable, and the thiamine group for the total bilirubin variable, it does not show a normal distribution for these thiamine groups but control and alcohol groups show normal distribution. In this case, one-way anova was applied to the normally distributed variables. While the thiamine group did not show normal distribution, the nonparametric kruskal wallis test was applied for 3 variables.

RESULTS

At the end of the study, while serum total bile acid, total bilirubin and insulin hormone levels increased in rats in the alcohol group compared to the rats in the control group; total protein and albumin values decreased ($P<0.05$). In the thiamine + alcohol group, LDL-C, total-C, bile acid levels and AST enzyme activity increased, while ALT enzyme activity and total protein levels decreased compared to the control group ($P<0.05$) (Table 1). In addition, there was no significant difference between the groups in serum glucose, triglycerides, HDL-C values and ALP enzyme activity (Table 1).

DISCUSSION

Chronic or acute alcohol consumption is known to damage various organs (Dguzeh et al., 2018). Since 95% of the alcohol consumed is metabolized in the liver, it has been proven that liver damage due to chronic and acute alcohol consumption is caused by the change in oxidative and energy metabolism in the liver (Lieber, 1997). These free radicals can damage numerous cellular components, primarily nucleic acids, lipids, and proteins. In this way, it contributes to the formation of many diseases, including alcoholic liver disease, by causing oxidative damage (Ward et al., 1989). There are agents that eliminate the harmful effects of oxidants and are described as antioxidants. While some of these agents are produced in the body endogenously, some of them must be taken exogenously from the diet (Bouayed et al., 2010). Vitamin B1, named as thiamine, belongs to the class of water-soluble vitamins that acts a significant role in energy metabolism, especially from carbohydrates (Portari et al., 2016). On the other hand, thiamine interacts with free radicals and hydroperoxides, preventing lipid perox-

Table 1. Serum biochemical parameters and serum insulin hormone levels.

Parameters	Control	Alcohol	Thiamine+Alcohol
Glucose (mg/dL)	272.55 ± 11.93 [a]	279.17 ± 19.96 [a]	281.73 ± 21.18 [a]
Triglycerides (mg/dL)	63.12 ± 2.95 [a]	58.71 ± 7.06 [a]	66.37 ± 7.02 [a]
Total Cholesterol (mg/dL)	64.86 ± 2.73 [a]	69.43 ± 1.98 [ab]	75.59 ± 2.36 [b]
HDL-C (mg/dL)	25.17 ± 0.70 [a]	21.83 ± 1.51 [a]	23.17 ± 0.98 [a]
LDL-C (mg/dL)	27.06 ± 2.29 [a]	35.85 ± 2.47 [ab]	33.80 ± 2.13 [b]
ALT (U/L)	95.60 ± 7.25 [a]	78.75 ± 5.89 [ab]	71.64 ± 5.36 [b]
AST (U/L)	127.85 ± 26.51 [a]	221.35 ± 14.43 [ab]	252.63 ± 36.58 [b]
ALP (U/L)	318.33 ± 6.28 [a]	204.83 ± 19.68 [a]	257.33 ± 60.51 [a]
Bile Acid (umol/L)	109.36 ± 6.91 [a]	131.50 ± 5.69 [b]	132.18 ± 5.12 [b]
Total Protein (g/dL)	7.23 ± 0.12 [a]	6.59 ± 0.20 [b]	6.25 ± 0.08 [b]
Total Bilirubin (mg/dL)	0.04 ± 0.01 [a]	0.09 ± 0.02 [b]	0.09 ± 0.01 [ab]
Albumin (g/dL)	3.83 ± 0.18 [a]	3.08 ± 0.05 [b]	2.93 ± 0.06 [b]
Insulin (umol/L)	2.05 ± 0.27[a]	2.54 ± 0.29[b]	2.44 ± 0.26[b]

idation and free radical oxidation in the liver (Lukienko et al 2000). Thiamine supplementation is used in thiamine deficiency, which is seen especially in alcoholics, due to poor eating habits and decreased absorption in the intestines (Lemos et al., 2005, Tallaksen et al., 1993).

In this study, we aimed to research the effects of thiamine treatment against the deterioration in some serum biochemical parameters and insulin secretion caused by acute alcohol administration in rats, an experimental model that produces effects similar to the effects caused by excessive alcohol ingestion in humans.

There are studies showing that acute alcohol consumption has no effect on blood glucose levels in humans (Schrieks et al., 2015; Steiner et al 2015). Indeed, a meta-analysis study showing alcohol consumption (10-70 kg/day) has no effect of in healthy individuals also supports this result (Schrieks et al., 2015). A cohort study shows that binge drinking causes higher fasting plasma glucose levels in men compared to women. Again, in the same study, it was reported that the highest blood glucose level associated with alcohol consumption among women aged 16-43 was in women aged 43 years (Nygren et al., 2017). On the other hand, in a study with rats, healthy and diabetic rats were given alcohol for 30 days. It has been reported that alcohol administration significantly increased blood glucose levels in diabetic rats, but there was no significant change in the healthy group (Shanmugam et al., 2011). In the current study, no significant change was observed in the blood glucose levels of healthy rats in which the binge drinking model was created (Table 1).

In one study, mice were administered with a chronic and binge drinking protocol, and compared with the control group, the alcohol group had a significant increase in serum activities of alanine aminotransferase (ALT), triglycerides, and LDL-C (Liu et al., 2014). It is well established that binge drinking is associated with an increase in LDL-C of approximately 10%, with an increased risk of atherosclerosis (Wood et al., 1998). In the current study, serum total cholesterol and LDL cholesterol increased after the binge drinking protocol. In a cohort study conducted by Al-attas et al (2014), it was reported that total cholesterol values decreased in individuals with and without diabetes who were given thiamine supplementation for 3 months. In a study on rats with diabetes, it was reported that thiamine supplementation reduced plasma cholesterol and triglyceride levels. Thiamine had no effect on HDL-C in these rats (Babaei et al, 2004). In the current study, while total cholesterol levels increased, LDL-C decreased in animals given thiamine (Table 1).

In a study, serum protein and albumin levels were significantly higher in non-drinkers compared to moderate or heavy drinkers. Heavy drinkers had significantly lower serum protein and albumin levels than moderate drinkers. In addition, heavy and moderate drinkers have significantly higher total and direct bilirubin levels than non-drinkers (Ebuehi and Asonya, 2007). Another study also reported that acute consumption of alcohol increases serum bilirubin levels in humans (O'Malley et al., 2015).

Indeed, in our study, serum protein and albumin levels were decreased and the total bilirubin levels were increased in the alcohol group according to control group. However, in the current study, thiamine administration did not significantly affect total protein, albumin, and total bilirubin values (Table 1).

In Ebuehi and Asonya (2007)'s study, serum AST, ALT, and ALP activities were significantly lower in control group than in moderate or heavy alcohol drinkers. The AST, ALT, and ALP enzyme activities of heavy drinkers were significantly higher than those of moderate drinkers. The predominance of AST

enzyme activity over ALT enzyme activity in alcoholic liver disorder was first studied in 1967 and the importance of a high AST/ALT ratio for the alcoholic liver disorder was reported. (Harinasuta, 1967). It has been reported that a decrease in hepatic ALT activity is among the causes of the high AST/ALT ratio in alcoholic liver disease (Maltoff et al., 1980). In the current study, ALT enzyme activity decreased and AST enzyme activity increased, and the AST/ALT ratio increased in the alcohol group (Table 1). In the study of Portari et al. (2013), administration of thiamine to rats administered alcohol caused a decrease in serum ALT and AST enzyme activities. In the current study, while increased AST enzyme activity was observed in the thiamine group, ALT enzyme activity decreased (Table 1).

On the other hand, it has been reported that alcohol intake increases serum bile acid levels in some studies (Donepudi et al., 2017; Manley and Ding, 2015). In the current study, it is seen that elevated bile acid levels in the alcohol and alcohol+thiamine group compared to the control group (Table 1). The role of bile acids in glucose metabolism also have been supported by a correlation between altered serum/plasma bile acid levels in metabolic changes such as obesity. Studies have shown that increased serum/plasma bile acids levels impair insulin sensitivity (Syring et al, 2019). As a matter of fact, it has been reported that serum bile acid levels are increased in insulin-resistant rats and mice (Shapiro et al, 2018).

Many studies show that acute alcohol consumption increases plasma insulin concentration, while alcohol acutely decreases insulin-stimulated glucose uptake in the whole body (Yki et al., 1988; Avogaro et al., 1996). There are studies showing that acute overdose of alcohol also causes insulin resistance in rats (Spolarics et al., 1994; Dhillon et al., 1996). Indeed, in our study, it was observed that an overdose of alcohol had higher insulin levels than healthy animals, but it did not affect the serum glucose level, and there was insufficient insulin activity (Table 1). On the other hand, in order to investigate the protective effect of thiamine, insulin levels decreased in the alcohol group to which thiamine was administered, although it was not statistically significant compared to the alcohol group.

CONCLUSION

In rodents with a binge drinking pattern, serum biochemical values are adversely affected, as in humans who drink heavily. In addition, it has been observed that the administration of thiamine vitamin, which is deficient in alcohol use and metabolic disorders occur due to this deficiency, during and before the acute use of alcohol has no effect on the changing biochemical parameters. Therefore, longer-term studies may be needed to determine the effects of thiamine on alcohol use.

DECLARATIONS

Ethics Approval

This study was approved by Burdur Mehmet Akif Ersoy University Rectorate, Animal Experiments Local Ethics Committee (Decision No: 688/2020).

Conflict of Interest

There is no conflict of interest.

Consent for Publication

Not applicable

Author contribution

Idea, concept, and design: HEE

Data collection and analysis: HEE

Drafting of the manuscript: HEE

Critical review: HEE

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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