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RESEARCH ARTICLE

Electrocardiographic Evaluation the Effect of Thiamine Hydrochloride on Triton X-100 Induced Hyperlipidemia in Rats

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Sıçanlarda Triton X-100'ün Neden Olduğu Hiperlipidemi Üzerine Tiamin Hidroklorürün Etkisinin Elektrokardiyografik Olarak Değerlendirilmesi

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Öz

Amaç: Hiperlipidemi, dünya genelinde yaygın bir durum olup kardiyovasküler hastalıklara önemli katkıda bulunur. Bu çalışma, Triton X-100 ile indüklenen hiperlipidemili ratlarda tiamin hidroklorürün lipid profilleri ve EKG değişiklikleri üzerindeki etkilerini araştırmaktadır.

Gereç ve Yöntem: On sekiz erkek Wistar Albino sıçanı üç gruba ayrıldı: Kontrol, Triton X-100 ve Triton X-100 + Tiamin. Hiperlipidemi, Triton X-100 (100 mg/kg, tek doz, intraperitoneal) kullanılarak indüklendi. Hiperlipidemi indüksiyonundan yetmiş iki saat sonra, tiamin hidroklorür, 7 gün boyunca günde 25 mg/kg dozunda intraperitoneal olarak uygulandı. EKG verileri kaydedildi ve serum biyokimyasal parametreleri analiz edildi.

Bulgular: Tiamin tedavisi, Triton X-100 ile indüklenen yüksek total kolesterol ve trigliserid seviyelerini önemli ölçüde azalttı. Ayrıca koroner risk indeksini iyileştirdi ve kalp hızı ile RR aralığı gibi EKG parametrelerini normale döndürdü. ST segment yükselmesi ve atriyal fibrilasyon gibi EKG anormallikleri, tiamin tedavisi uygulanan grupta daha az sıklıkla gözlendi.

Öneri: Tiamin hidroklorür, hiperlipidemiyi ve buna bağlı kardiyovasküler riskleri etkili bir şekilde hafifletmekte olup, terapötik bir ajan olarak potansiyelini göstermektedir. Dislipidemi ve kardiyovasküler hastalıkların yönetiminde klinik uygulamaları derinlemesine anlamak için ek bilgi ve araştırma gereklidir.

Anahtar kelimeler: Elektrokardiyografi (EKG), Hiperlipidemi, Lipid profilleri, Tiamin hidroklorür, Triton X-100

Abstract

Aim: Hyperlipidemia, a prevalent condition globally, contributes significantly to cardiovascular diseases. This research focuses on the impacts of thiamine hydrochloride on lipid profiles and ECG changes in rats with Triton X-100-induced hyperlipidemia.

Materials and Methods: A total of eighteen male Wistar Albino rats were divided into three groups: control, Triton X-100, and Triton X-100 + Thiamine. To induce hyperlipidemia, Triton X-100 was administered as a single intraperitoneal dose of 100 mg/kg. Thiamine hydrochloride was then given intraperitoneally at a dose of 25 mg/kg daily for 7 days, starting 72 hours after the induction of hyperlipidemia. ECG data were recorded, and serum biochemical parameters were analyzed.

Results: Thiamine treatment significantly reduced elevated total cholesterol and triglyceride levels induced by Triton X-100. It also improved the coronary risk index and normalized ECG characteristics include the heart rate and the RR interval. ECG abnormalities, including ST segment elevation and atrial fibrillation, were less frequent in the thiamine-treated group.

Conclusion: Thiamine hydrochloride effectively mitigates hyperlipidemia and its associated cardiovascular risks, suggesting its potential as a therapeutic agent. Further research is needed to explore its clinical applications in managing dyslipidemia and cardiovascular diseases.

Keywords: Electrocardiography (ECG), Hyperlipidemia, Lipid profiles, Thiamine hydrochloride, Triton X-100

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Introduction

Hyperlipidemia, a widespread illness globally, is a major risk factor for obesity, stroke, myocardial infarction, atherosclerosis, type 2 diabetes, and circulatory disorders. It is biochemically marked by elevated cholesterol and triglyceride levels (Hashem et al., 2021). Sedentary lifestyles, poor diets, and diseases such as hypertension, diabetes, dyslipidemia, and obesity are all significant risk factors for cardiovascular disease. Hyperlipidemia is a primary marker for atherosclerosis, which involves lipid accumulation, mainly cholesterol, in the arterial walls (Wojtasinska et al 2023).

Although hyperlipidemia can be asymptomatic, long-term hypercholesterolemia increases the risk of cardiovascular diseases (Nelson 2013). Many animal models, mainly using diet-induced methods, replicate this condition to study its effects. Mice and rats, naturally resistant to atherosclerosis, become more susceptible through dietary and genetic manipulations (Andreadou et al 2020). It is also typical practice to use chemicals such as Triton X-100, WR-1339, cholesterol, poloxamer 407, and methionine for chemical induction (Hashem et al 2021). The nonionic surfactant Triton X-100 enhances intestinal lipid absorption and hepatic cholesterol production, while inhibiting lipoprotein lipase, leading to elevated blood lipid levels (Kumar et al 2010, Parwin et al 2019).

Early diagnosis and detection of cardiovascular diseases, facilitated by electrocardiography (ECG), can prevent many deaths (Hammad et al 2018). The ECG monitors the heart's electrical activity, detecting anomalies, conduction issues, rhythm disorders, and effects of medications and chemicals. High-fat diet-induced hyperlipidemia in mice has shown significant changes in ECG waveforms, particularly increased T wave duration, RR, and QT intervals (Maulana et al 2023).

Treating hyperlipidemia effectively and safely remains a challenge, especially with current drugs' limitations in addressing lipoprotein disorders. Recent studies explore vitamins' potential in managing hyperlipidemia (Catalgol and Ozer 2012, Csont et al 2013, Liu et al 2020).

Thiamine (Vitamin B1) is particularly interesting for its role in glucose metabolism and insulin action (Mrowicka et al 2023). The gastrointestinal tract absorbs this water-soluble vitamin, which then circulates through the bloodstream and is excreted in the urine. The liver, heart, kidneys, and brain all store small quantities of thiamine temporarily. Thiamine diphosphokinase is the enzyme responsible for converting thiamine into its active form, thiamine pyrophosphate (TPP), which is crucial for glycolysis, the Krebs cycle, and the pentose phosphate pathway. TPP assists enzymes in metabolizing carbohydrates, lipids, and branched-chain amino acids (Sriram et al 2012). Thiamine deficiency is associated with various cardiovascular diseases and risk factors, including dyslipidemia, heart failure, myocardial infarction, and depression. Increasing evidence links thiamine deficiency directly or indirectly with dyslipidemia (Eshak and Arafa 2018). Growing evidence suggests that vitamin B1 supplementation can help reverse cardiovascular issues such as dyslipidemia in patients (Wen et al 2023). High-dose thiamine supplementation may positively affect blood pressure and lipid profiles in individuals with hyperglycemia (Alaei-Shahmiri et al 2015). Additionally, thiamine deficiency can lead to cardiac conduction abnormalities observable through ECGs, worsening conditions like dyslipidemia and increasing cardiovascular risks and ECG alterations (Eshak and Arafa 2018). The research on rats suggests that thiamine hydrochloride pretreatment before doxorubicin delivery reduces oxidative stress, enhances cardiac contractility, and strengthens antioxidant defenses, the precise effects of thiamine on the cardiovascular system remain poorly understood (Radonjic et al 2020).

Although there are a limited number of experimental studies on the effect of thiamine on cardiovascular disorders related to dyslipidemia, no research has investigated the protective effects of thiamine hydrochloride on Triton X-100-induced dyslipidemia in rats. Most existing data come from human studies. Our study hypothesizes that thiamine hydrochloride could enhance current knowledge by assessing its potential effects on the electrocardiogram (ECG) in a chemical dyslipidemia model induced by Triton X-100. This study aimed to investigate how thiamine hydrochloride influenced changes in ECG data in rats with experimental hyperlipidemia induced by Triton X-100.

Material and Methods

The Sivas Cumhuriyet University Animal Experiments Local Ethics Committee approved the study to be conducted on eighteen male Wistar Albino rats, weighing between 220-240 g and aged 10-12 weeks (Approval No: 2023/06). The Sivas Cumhuriyet University Experimental Animals Application and Research Center provided the animals used in the study with standard care conditions, including adequate ventilation, a 12-hour light/dark cycle, a temperature range of 21–23°C, and a humidity level of 35–60%. They were also fed a diet of pellet rat feed and water on demand. Following a week-long period of adaption, the rats were divided into three groups at random (n = 6/group).

Control group: Rats in this group were provided with water and standard rat food ad libitum, without any additional treatment.

Triton X-100 group: After an 18-hour overnight fast, Wistar albino rats received a single intraperitoneal injection of

a freshly prepared Triton X-100 solution (100 mg/kg) in sterile saline. Sterile saline was injected intraperitoneally 72 hours after induction of hyperlipidemia and continued daily for 7 days (Shafik et al 2017).

Triton X-100+Thiamine group: After an 18-hour overnight fast, Wistar albino rats received a single intraperitoneal injection of freshly prepared Triton X-100 solution (100 mg/kg) in sterile saline. Thiamine hydrochloride (Solgar, New Jersey, USA) was administered intraperitoneally at a dose of 25 mg/kg daily for 7 days, starting 72 hours after the induction of hyperlipidemia (Radonjic et al 2020, Rankovic et al 2021).

At the beginning and end of the study, the live weights of the rats were measured. Twenty-four hours after the last thiamine hydrochloride administration, ECG recordings were taken under solid anesthesia with ketamine (90 mg/kg) and xylazine (3 mg/kg) using a Televet II ECG device (Kruuse, Germany) in the Einthoven mode in Lead II for 5 minutes using crocodile electrodes. The recordings were analyzed using a software program (Televet 100 Version® 7.0.0, Kruuse, Heusenstamm, Germany). The heart rate (bpm), the amplitude of the R wave (mV), the PR, RR, QT, and QTc intervals (ms), and other ECG data were analyzed. Blood was extracted from the heart while under anesthesia following the recording of the ECG, and serum samples were obtained by centrifuging the blood for 10 minutes at 4000 rpm. As per the kit's instructions, photometric techniques were used to measure triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) using an autoanalyzer (Cobas 8000 C702, Roche, Mannheim, Germany). Both the coronary risk index (CRI) and the atherogenic index (AI) were determined. Here is how AI and CRI were determined: LDL/HDL is equal to AI, and total cholesterol/HDL to CRI (Shafik et al 2017).

Statistical Analysis

GraphPad Prism Version 10.2.3 was utilized for data analysis upon completion of the study, employing one-way ANOVA followed by the post hoc Tukey test. Results were graphically presented as mean ± standard error. A significance level of $P<0.05$ was considered statistically significant.

Results

There were no noticeable variations between the groups ($P>0.05$) in the measurement of the rats' initial body weights (Control: 227 ± 3.09 g, Triton X-100: 230.2 ± 1.28 g, Triton X-100+Thiamine: 232.2 ± 0.80 g) and final body weights (Control: 217 ± 3.37 g, Triton X-100: 226.7 ± 2.84 g, Triton X-100+Thiamine: 226.3 ± 5.39 g) (Figure 1). Similarly,

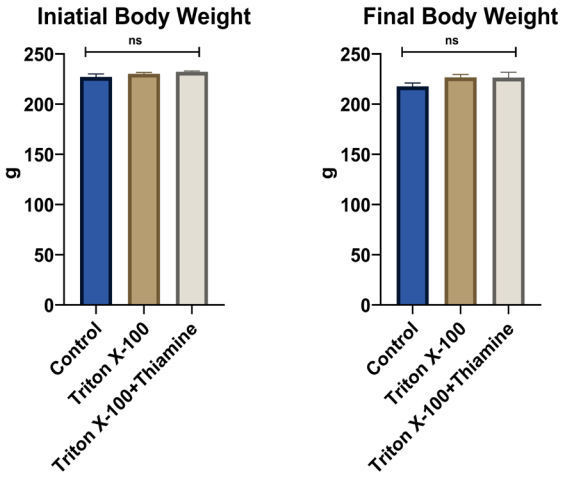

Figure 1. Experimental initial and final changes in live weights of rats. Effect of thiamine treatment on weight change in rats with hyperlipidemia induced by Triton X-100: A graph showing the results at the end of the experiment compared to the initial weight. ns: Not significant.

there were no significant changes ($P>0.05$) between the groups in the study of liver-related enzyme concentrations among the biochemical parameters (Figure 2). Serum AST concentrations were found to be 92.08 ± 8.98 U/L in the Control group, 99.03 ± 4.50 U/L in the Triton X-100 group, and 100.1 ± 15.41 U/L in the Triton X-100+Thiamine group. Serum ALT concentrations were recorded as follows: Control: 35.85 ± 3.26 U/L, Triton X-100: 34.45 ± 3.32 U/L, and Triton X-100+Thiamine: 32.98 ± 3.14 U/L. Additionally, serum ALP concentrations were measured as: Control: 95.50 ± 6.76 U/L, Triton X-100: 91.50 ± 9.87 U/L, and Triton X-100+Thiamine: 81.20 ± 5.27 U/L.

However, blood total cholesterol levels were considerably higher in the Triton X-100 group (59.76 ± 4.38 mg/dL) than in the control group (40.00 ± 8.39 mg/dL) ($P>0.05$). In contrast, thiamine therapy significantly lowered high total cholesterol levels (31.33 ± 1.67 mg/dL) ($P<0.01$). Similarly, the Triton X-100 group (119.0 ± 9.02 mg/dL) had significantly greater blood triglyceride levels than control group (62.83 ± 7.12 mg/dL) ($P<0.01$). Thiamine therapy considerably lowered high triglyceride levels (81.50 ± 7.27 mg/dL) ($P<0.05$). The Triton X-100 (32.44 ± 2.34 mg/dL) and Triton X-100+Thiamine groups (26.40 ± 2.02 mg/dL) had significantly reduced blood HDL levels compared to the control group (50.78 ± 3.26 mg/dL) ($P<0.01$, $P<0.001$). However, the Triton X-100+Thiamine group (3.38 ± 0.55 mg/dL) had considerably reduced serum LDL concentrations compared to the Triton X-100 (5.24 ± 0.46 mg/dL) group ($P<0.05$). The Triton X-100 group had considerably greater atherogenic and coronary risk indexes than the control group ($P<0.05$ and $P<0.001$, respectively). However, thiamine treatment significantly reduced only the coronary risk index ($P<0.05$) (Figure 3).

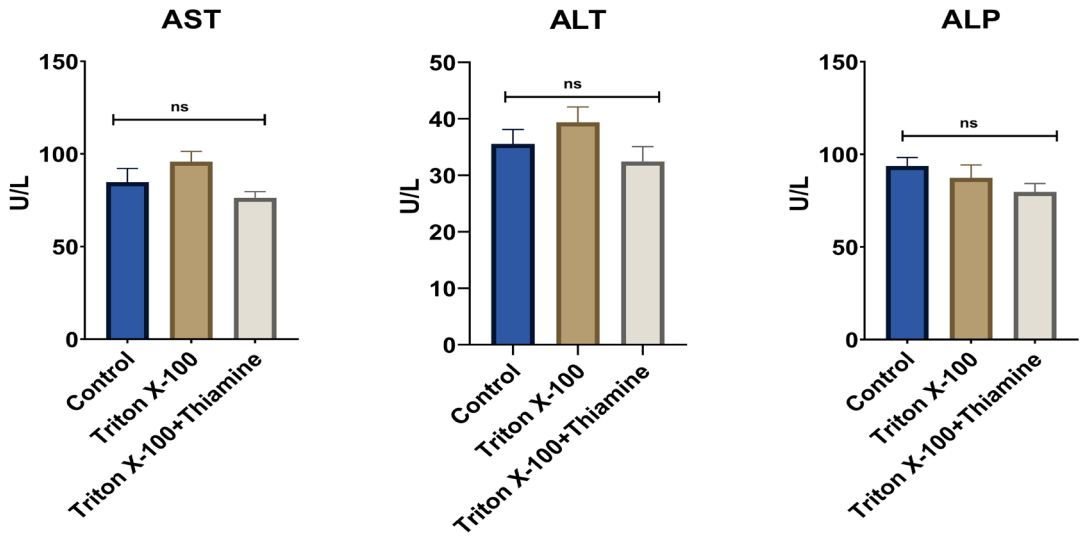

Figure 2. Effect of thiamine hydrochloride on liver function tests in rats administered Triton X-100. Serum levels of AST, ALT, and ALP were measured using an autoanalyzer (Cobas 8000 C702, Roche, Mannheim, Germany). ns: Not significant.

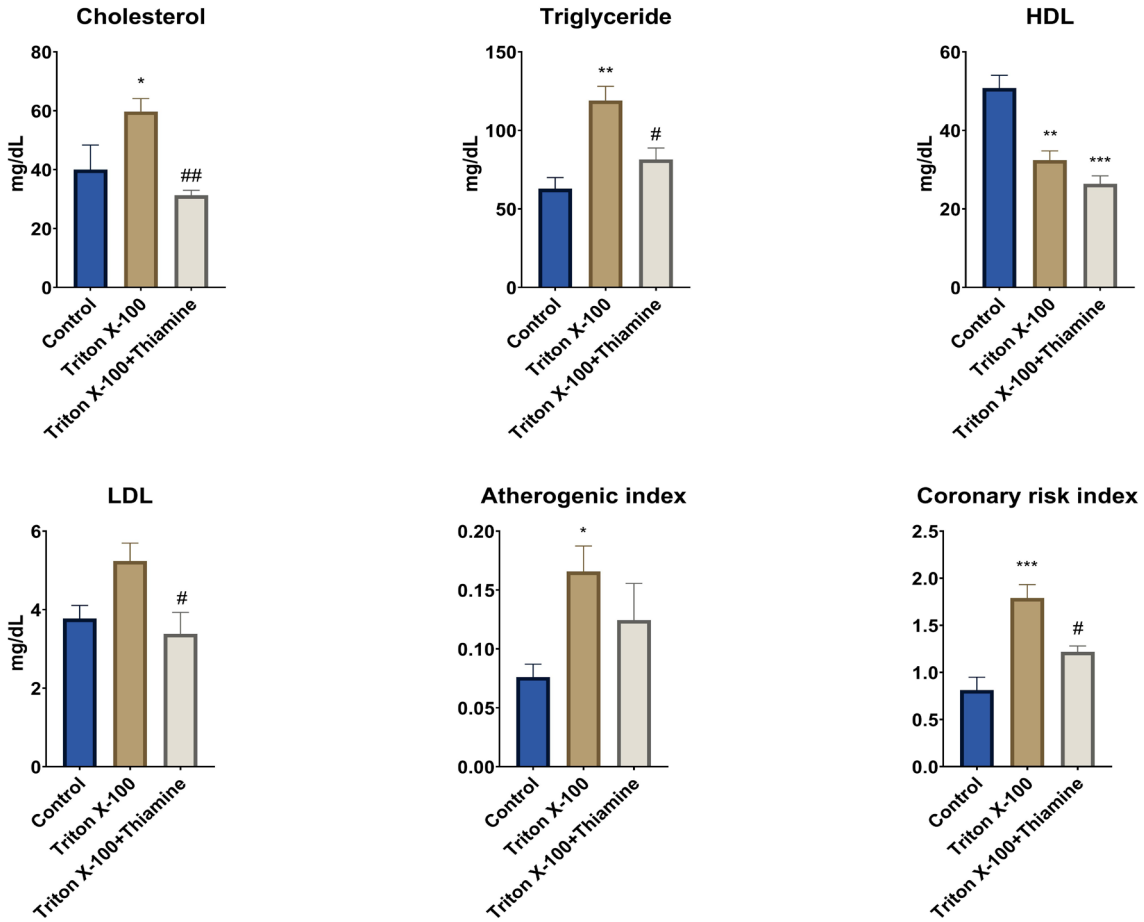

Figure 3. Effect of thiamine hydrochloride on lipid profile, atherogenic index, and coronary risk index in Triton X-100-administered rats. ns: Not significant. *P<0.05, **P<0.01, ***P<0.001 denote significance compared to the Control group; #P<0.05, ##P<0.01 denote significance compared to the Triton X-100 group.

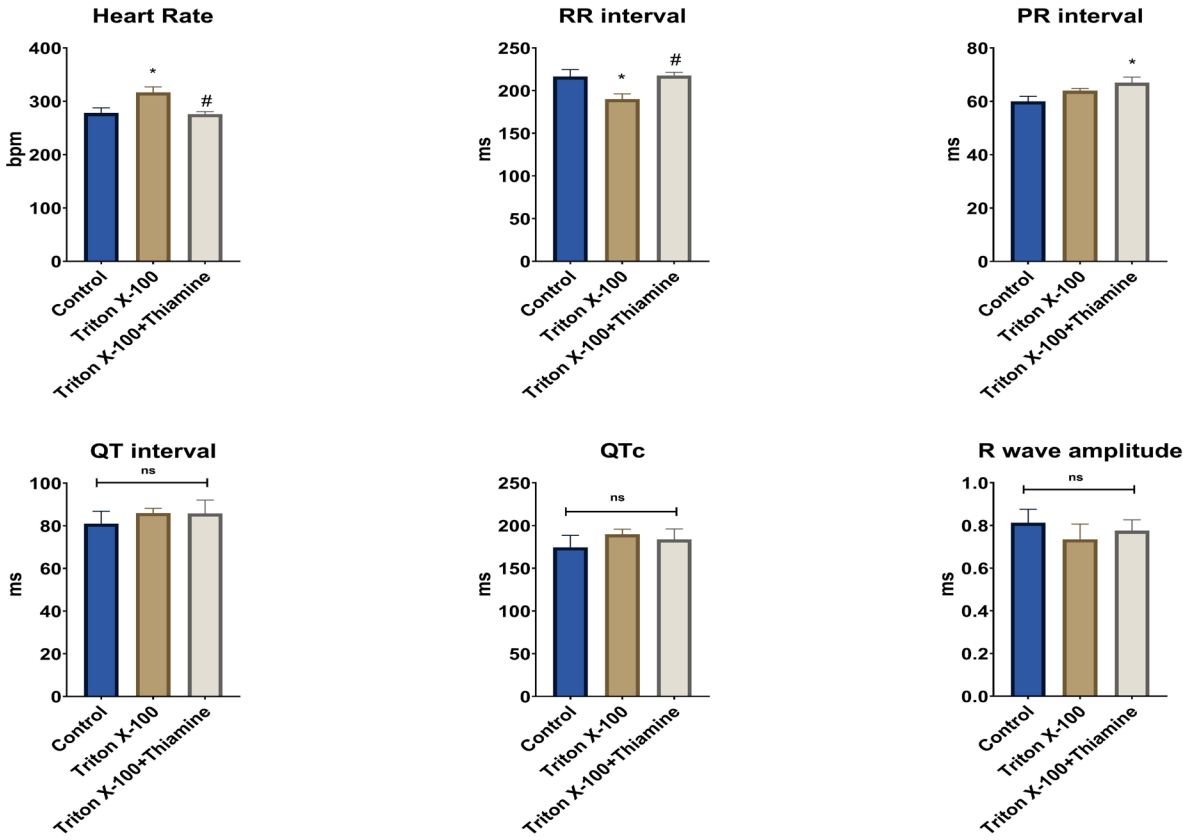

Figure 4. Effect of thiamine hydrochloride on ECG data in Triton X-100-administered rats. ns: Not significant. *P<0.05 denote significance compared to the Control group; #P<0.05 denote significance compared to the Triton X-100 group.

Based on previously published research, it was observed that the majority of the ECG data from the control group fell within the reference range (Konopelski and Ufnal 2016). The Triton X-100 group's heart rate (316.8 ± 10.23 bpm) was much greater than the control group's (278.0 ± 9.76 bpm) in the ECG data analysis (P<0.05). In contrast, in the same group compared to the control group (216.5 ± 8.10 ms), the RR interval was significantly shorter (190.0 ± 6.16 ms) (P<0.05). Relative to the Triton X-100 group, thiamine treatment dramatically raised the RR interval (217.6 ± 3.76 ms) and decreased heart rate (276.0 ± 4.79 ms) (P<0.05). In the analysis of the PR interval, it was found to be significantly prolonged in the Triton X-100+Thiamine group (67.00 ± 2.05 ms) compared to the control group (60.00 ± 1.83 ms) (P<0.05). On the other hand, the QT interval, QTc interval, and R wave amplitude did not show statistically significant differences across the groups (P>0.05) (Figure 4). Additionally, rats treated with Triton X-100 alone showed findings such as ST segment elevation, T wave elevation, atrial fibrillation, and low amplitude P waves, while these findings were observed less frequently in rats treated with thiamine.

Discussion

Hyperlipidemia is regarded one of the most frequent variables causing cardiovascular illnesses, accounting for one-third of all fatalities worldwide (Jorgensen et al 2013). Currently, the effectiveness of synthetic hyperlipidemic drugs is being gradually reduced due to the emergence of treatment resistance and concomitant adverse effects. Therefore, experimental new therapeutic interventions are inevitable. This study investigated the effects of thiamine hydrochloride on lipid profiles and ECG changes in rats with Triton X-100 induced hyperlipidemia. The findings highlight thiamine's potential in mitigating hyperlipidemia and its associated cardiovascular risks, offering promising insights into its therapeutic applications.

Consistent with other research, our study did not observe any statistically significant differences in body weight changes across the study groups (Shafik et al 2017). This may be related to the experimental design or the adaptation and acclimation of the rat organisms during the treatment period following hyperlipidemia induction. The search results do not provide specific information on the effects

of Triton X-100-induced hyperlipidemia on body weight changes in animals. The studies focus more on the protective or antihyperlipidemic effects of various compounds, such as alendronate, psyllium husk extract, and potato peel powder, against the Triton X-100-induced increase in blood lipid levels (Parwin et al 2019, Hashem et al 2021, Soltan et al 2023). More targeted research is needed to determine the direct impact of Triton X-100-induced hyperlipidemia on body weight in animal models.

Triton X-100 application in animal models leads to a significant increase in liver function test values such as AST, ALT, and ALP, indicating liver injury and dysfunction (Saleem et al 2017, Parwin et al 2019, Hashem et al 2021). The mechanism of Triton-induced hyperlipidemia involves penetration of fat into hepatocytes, resulting in hepatocellular damage (Shafik et al 2017). Furthermore, hepatocytes with excessive fat accumulation may become dysfunctional due to various mechanisms, including oxidative stress, lipid peroxidation, free fatty acids (FFAs), cytokine-induced hepatotoxicity, and mitochondrial dysfunction, potentially leading to liver failure (Fabbrini et al 2010). Hepatic cholesterol production has increased as a result of this condition, and plasma triglyceride accumulation has also risen. In our investigation, there were no statistically significant differences observed in the biochemical liver function tests among the experimental groups. Consistently, previous similar studies have reported that Triton X-100 did not have a significant effect on liver function tests such as serum AST and ALT in our study (Shafik et al 2017). Unlike other pre-treatment experimental procedures, the experimental design of this study ensured consistency with previous research, aligning our results accordingly. It can be suggested that during the treatment period of the post-treatment hyperlipidemia model, the liver may have been in a phase of tolerating the damage caused by a single dose of Triton X-100, and although there was tissue damage in the liver, it did not reflect in serum parameters at the end of the experiment.

Triton X-100 has been extensively shown to cause acute hyperlipidemia in animal models and to block the clearance of lipoproteins high in triglycerides and triacylglycerol (TAG) (Gundamaraju et al 2014, Parwin et al 2019). Triton X-100 injection causes the liver to secrete more VLDL, which raises plasma triglyceride and cholesterol levels. This is followed by a marked decrease in the catabolism of VLDL and LDL (Kellner et al 1951). Triton X-100 also raises blood lipid levels by inhibiting lipoprotein lipase activity, preventing extrahepatic organs from absorbing lipoproteins from the circulation. Elevated total cholesterol levels are linked to a higher risk of developing atherosclerosis. Notably, atherogenic indices are significant markers of heart disease risk, as elevated values are associated with a higher risk of cardiovascular disease and vice versa (Obidah Abert et al 2022). In our study, Triton X-100 increased serum cholesterol, triglyceride, and LDL levels, while decreasing serum HDL levels. Furthermore, Triton X-100 significantly increased the atherogenic index and coronary risk index. This suggests that all rats given a Triton X-100 injection experienced hyperlipidemia and dyslipidemia, as well as an elevated risk of cardiovascular issues (Gundamaraju et al 2014, Shafik et al 2017, Parwin et al 2019). In our study, thiamine alleviated Triton X-100-induced dyslipidemia and showed a tendency to improve the atherogenic and coronary risk index. Although high-dose thiamine treatment did not affect HDL levels in our investigation, a previous study highlighted that it protected against diabetic dyslipidemia in experimental diabetes, likely by reducing food intake and hexosamine pathway signaling (Babaei-Jadidi et al 2004). Another experimental study demonstrated that thiamine corrects dyslipidemia in rats, resulting in minimized microvascular and macrovascular complications of diabetes (Naveed et al 2009). TPP supplementation in diabetic rats significantly reduced triglycerides (TG), total cholesterol (TC), and the atherogenic index compared to untreated diabetic rats. In comparison to healthy controls who were not given therapy, the medication also reduced TG, TC, and the atherogenic index in healthy rats (Mahdavifard and Nakhjavani 2020). In a human trial, individuals with type 2 diabetes who received oral thiamine supplementation for six months (100 mg/day) showed a substantial improvement in their lipid profile, particularly with lower levels of total cholesterol and low-density lipoprotein (LDL) (Al-Attas et al 2014). Our study supports the notion that thiamine could be a therapeutic agent in the treatment of dyslipidemia and reduce cardiovascular risk. However, there is a need for comprehensive studies to further elucidate the effect of thiamine on dyslipidemia or hyperlipidemia and reduce cardiovascular complications.

An ECG examination is a diagnostic technique used to evaluate the heart's electrical activity. Few studies have examined the effects of dyslipidemia or hyperlipidemia on ECG readings. A recent experimental study reported significant changes in the durations of ECG waves in a rat hyperlipidemia model induced by a high-fat diet (Maulana et al 2023). At the end of the experiment, the study noted prolonged QT and RR intervals, as well as T wave duration, in the hyperlipidemia group compared to the control group, alongside a decreased heart rate (Maulana et al 2023). Another study reports that the decrease in heart rate variability parameters in a rat model of dyslipidemia induced by another high-fat diet is associated with increasing markers of lipid and atherosclerosis index with progressive severity of atherosclerosis. This is also reported to result in autonomic dysfunction (Kumar et al 2024). In another study, it was reported that there were no differences in the durations of PR, RR, QT, and QTc intervals in hyperlipidemic rats (induced with poloxamer 407)

based on ECG data (Patel and Brocks 2010). In our study, conducted on rats with hyperlipidemia induced by Triton X-100, it was reported that heart rate increased, RR interval decreased, while there were no differences observed in PR, QT, and QTc intervals, as well as in R wave amplitude. The recent our findings in Triton X-100-induced hyperlipidemia models support varied electrocardiographic outcomes across different hyperlipidemia models. Additionally, Triton X-100-induced hyperlipidemia modifies the heart system, particularly affecting autonomic functions, which indicate increased cardiovascular stress and heightened sympathetic activity. Thiamine treatment effectively normalized these parameters (heart rate and RR interval), suggesting its cardioprotective properties (Radonjic et al 2020, Rankovic et al 2021). The prolongation of the PR interval in the Triton X-100 + Thiamine group may indicate thiamine's influence on atrioventricular nodal conduction, warranting further investigation to elucidate its clinical significance. Rats treated with Triton X-100 alone exhibited significant ECG abnormalities, including ST segment elevation, T wave elevation, atrial fibrillation, and low-amplitude P waves. These findings are consistent with hyperlipidemia-induced cardiac stress and arrhythmias. In a previous study on rats, it was reported that rats with thiamine deficiency exhibited bradycardia, ST-segment elevation, and changes in the T wave on their electrocardiograms. These alterations were found to persist until thiamine was administered, after which they resolved (Weiss et al 1938). Thiamine treatment reduced the frequency and severity of these abnormalities, highlighting its potential to mitigate hyperlipidemia-induced cardiac dysfunction.

Our study has several limitations despite the encouraging outcomes. Firstly, the research was conducted using animal models, so caution must be exercised when applying the results to human populations. Furthermore, the specific mechanisms underlying thiamine's effects on lipid metabolism and cardiac function need more detailed exploration. Future studies should address these limitations to strengthen the understanding and potential therapeutic applications of thiamine in managing hyperlipidemia and cardiovascular diseases.

Conclusion

In conclusion, our study investigated the effects of thiamine hydrochloride on lipid profiles and ECG changes in rats with Triton X-100-induced hyperlipidemia. Thiamine treatment effectively normalized cardiac parameters and reduced ECG abnormalities associated with hyperlipidemia. These findings underscore thiamine's potential as a therapeutic agent for mitigating hyperlipidemia and its associated cardiovascular risks. Further research is warranted to fully elucidate thiamine's clinical implications in managing dyslipidemia and reducing cardiovascular complications.

Conflict of Interest

The authors declare no conflict of interest.

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Ethical Approval

Sivas Cumhuriyet University Animal Experiments Local Ethics Committee (Approval No: 2023/06).