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The Effect of Chronic Swimming Exercise and Vitamin E Supplementation on Bone Element Metabolism in Epileptic Rats

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ABSTRACT

Introduction: This study aimed to investigate the effects of chronic swimming exercise and vitamin E administration on elemental levels in the bone tissue of epileptic rats.

Methods: Forty-eight rats were divided into six groups: Control, Swimming, Swimming + vitamin E, Swimming + Epilepsy, Swimming + Epilepsy + vitamin E, and Epilepsy. Vitamin E was administered to the animals chronically by gavage at a dose of 500 mg/kg every other day for 3 months. Epileptiform activity was induced with penicillin in animals 24 hours after the last vitamin E intake. The exercise program consisted of daily 30-minute swimming sessions. At the end of the treatment period, the levels of calcium, chromium, copper, iron, magnesium, manganese, lead, and zinc (µg/gram tissue) in bone tissue samples were measured using an atomic emission device.

Results: The results showed that all epileptic groups had significantly lower bone chromium levels compared to the control groups ($p<0.05$). The epileptic, and epileptic swimming groups had the lowest levels of bone calcium, magnesium, and zinc ($p<0.05$). Vitamin E administration resulted in a significant increase in bone calcium, magnesium, and zinc levels in the epileptic swimming group with vitamin E compared to the epileptic and epileptic swimming groups. ($p<0.05$).

Conclusion: The findings of the study show that the administration of vitamin E improves calcium, magnesium, and zinc metabolism in the deteriorated bone tissue of the epileptic rat model.

Keywords: Bone elemental metabolism, epilepsy, rat, swimming exercise, vitamin E

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INTRODUCTION

Epilepsy is a neurological condition characterized by abnormal brain activity, often leading to unconsciousness and unusual behaviors (1). At the same time, epilepsy is a global public health problem that affects approximately 70 million people around the world and 100 thousand people are added to this figure every year (2,3). Although it is known that environmental and genetic factors are associated with epilepsy, the basic pathological mechanisms leading to epilepsy have not been fully elucidated (2,3).

There is increasing evidence in the literature that epilepsy and its treatment may be associated with bone health. The risk of fractures is 2–3 times higher in individuals with epilepsy (4). The increased risk of fractures in individuals with epilepsy can be attributed to seizures that cause falls and strain on the bones, as well as the potential effects of antiepileptic drugs themselves (possibly causing bone mineral deficiency, sedation, or creating balance problems when taken in high doses) (4). In comparison to a group of 120 healthy controls, adult patients undergoing antiepileptic drug treatment showed decreased ionized calcium values, increased parathormone concentrations, and a decline in bone element metabolism. (5). The use of antiepileptic drugs has already been associated with decreased bone mineral density (6). However, an increase in non-traumatic fractures has been reported in patients with epilepsy (7). It has been reported that patients with tonic-clonic seizures have a higher risk of fractures, suggesting that the type of epileptic seizure influences fracture risk (5). It has been shown that both the duration and type of epilepsy contribute to an increased risk of fractures (8). Patients with epilepsy not only face an elevated risk of fractures but also exhibit a significant decrease in bone mineral density (7). Neurological disorders accompanying epilepsy impose limitations on physical activity, which is another factor affecting bone metabolism in individuals with epilepsy (4).

Highlights

- **Epilepsy leads to changes in bone element metabolism.**
- **Chronic exercise does not improve bone metabolism that is impaired in epilepsy.**
- **Vitamin E supplementation effectively improves bone element metabolism in epilepsy.**

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It has been reported that children and adolescents with epilepsy may experience prolonged seizures during sports activities (9). For this reason, people with epilepsy are advised not to participate in sports and exercise. However, the available evidence shows that; physical exercise or active sports can maintain good health, provide psychosocial benefits, and positively affect seizure control (10). However, when recommending sports to individuals with epilepsy, it is important to consider sports activities that do not pose additional risks in the event of a seizure, which could lead to potential injury or death (11). From this perspective, it is advisable to encourage individuals with epilepsy to engage in physical exercise and sports by considering appropriate sports branches (9).

It has been reported that vitamin E administration, known for its antioxidant activity, can reduce seizures in a rat epilepsy model (11). It has also been reported that vitamin E supplementation may have a regulatory effect, albeit limited, on impaired brain element metabolism in epileptic rats (12).

In recent years, there has been an increasing interest in investigating the relationship between bone metabolism abnormalities and epilepsy (13). Investigating impaired bone and element metabolism in epilepsy can aid in identifying patients at risk, thereby facilitating the planning of prophylactic and therapeutic measures.

Due to the limitations and challenges of studying epilepsy in humans, researchers often rely on animal models, with the penicillin model being one of the most widely used. The aim of this study is to investigate the effect of chronic swimming exercise and vitamin E administration on the levels of elements in the bone tissue of rats with epilepsy.

METHODS

The experimental stages of this study were conducted on Wistar adult male rats at the Ondokuz Mayıs University Experimental Medicine Research and Application Center. The subsequent analysis stages were performed at Selcuk University. The study protocol was approved by the Animal Experiments Local Ethics Committee of Ondokuz Mayis University (2010/36). A total of 48 rats were used, and they were evenly divided into 6 groups.

Study Groups

Rats were divided into six groups as follows:

Group 1, Control: This group did not receive any specific intervention.

Group 2, Swimming: This group underwent swimming exercises for half an hour per day over a three-month period.

Group 3, Swimming with Vitamin E: This group participated in half an hour of swimming exercise per day for three months, and in addition, they received 500 mg/kg of vitamin E administered via the gavage method every other day for the same three-month period.

Group 4, Epileptic Swimming: In this group, the rats underwent half an hour of swimming exercise per day for three months, and epileptiform activity was induced 24 hours after the last swimming exercise.

Group 5, Epileptic Swimming with Vitamin E: This group participated in half an hour of swimming exercise per day for three months, and in addition, they received 500 mg/kg of vitamin E administered via the gavage method every other day for the same three-month period.

Epileptiform activity was induced in animals 24 hours after the last vitamin E administration.

Group 6, Epilepsy: This group served as the epileptic control group with established epileptiform activity.

Experimental Animals

The experimental animals were kept in an environment with 12 hours of darkness, 12 hours of light, and a standard room temperature (21±1°C). The animals in groups 3 and 5 received 500 mg/kg of vitamin E by the gavage method every other day for a duration of 3 months. All procedures, including swimming exercises, were conducted within the time frame of 10 AM to 12 PM. Following the experimental applications, bone tissue samples were collected from the sacrificed animals. The bone (femur) tissue samples were stored at -35°C until analysis.

Experimental Applications

Swimming Exercise

The exercise was conducted in a heat-resistant, glass swimming pool measuring 90×45×45 cm. The swimming pool was equipped with a thermostat to maintain a constant temperature of 32–33°C. The swimming exercises were conducted daily for 30 minutes, each taking place between 10 AM and 12 PM for 90 days. It is accepted that swimming exercises lasting between 30 minutes and 60 minutes induce a moderate level of stress in rats (14). Therefore, in our study, we specifically programmed the swimming exercise duration to be 30 minutes in order to minimize potential stress factors for the rats. Swimming exercises were conducted in pairs. Twenty-four hours after the completion of the ninety-day swimming period, the rats were prepared for the induction of epileptiform activity.

Surgical Procedures and Penicillin Administration

The rats, following a 12-hour fasting period, were anesthetized by intraperitoneal (IP) administration of 1.2 g/kg of urethane. The hair on the top of the rats' heads was shaved, and the rats were then secured to the operating table. A rostro-caudal incision of approximately 3 cm in length was made to open the scalp of the animal. Electrocautery was used to prevent any bleeding that may occur in the soft tissue. The soft tissue on the left somatomotor cortex was removed, the skull was thinned with a motor and the skull bone was carefully removed. To prevent any potential bleeding in the bone tissue during this procedure, bone wax was applied. To prevent heating caused by friction, saline-impregnated sponges were intermittently applied to the skull during the procedure. After the skull bone was completely removed, the dura mater was carefully removed (12).

Penicillin G Potassium was administered at a dosage of 1 million units (solvent: distilled water). For the induction of epileptiform activity, Penicillin was administered intracortically (ic) at a dose of 500 units (IU) and a volume of 2.5 µl (Penicillin infusion rate: 0.5 µl/min) (12).

Epileptic activity was monitored electrophysiologically with a four-channel recorder (PoweLab 4/SP) for 3 hours. Epileptic activity was observed to appear within 2–5 minutes and reached a steady state at 30 minutes. Following this, rats were sacrificed 3 hours later. The epilepsy-related records pertaining to this study were excluded from the current research as they had been previously prepared for use in another publication. However, another study conducted by the same group of authors, which examined the correlation between epilepsy and exercise, was referenced to provide an example of epileptic activity records in the current study (15).

Bone (Femur) Tissue Elemental Analysis (calcium, chromium, copper, iron, magnesium, manganese, lead, and zinc)

Bone (femur) tissue samples were collected from the rats and placed into polyethylene mouth-cap tubes that had been washed with NHO_3 and deionized water to prevent contamination. The tissue samples were stored at -35°C until the day of analysis. The analysis procedures were conducted using an Atomic Absorption Spectrophotometer (AAS Varian AA240FS) device, and the results were calculated as µg/gram tissue.

Statistical Evaluations

The data were statistically evaluated using the IBM Statistical Package for Social Sciences (SPSS) program version 21.0 computer package program, and the arithmetic means and standard deviations of all values were determined. The "Shapiro-Wilk" test was used to assess the homogeneity of the data, and it was discovered that the data did not have a normal distribution. The Kruskal-Wallis H test was used to discover group differences, while the Mann-Whitney U test was used to establish which group was responsible for the observed differences. Differences at the $p<0.05$ level were considered significant.

RESULTS

The epileptic (G6) and epileptic swimming (G4) groups exhibited significantly lower bone calcium values compared to the other groups ($p<0.05$).

In the epileptic swimming with vitamin E group (G5), the administration of vitamin E resulted in a significant increase in bone calcium levels, reaching similar levels as the control group ($p<0.05$, Figure 1). In all epilepsy groups (G4, 5 and 6), bone chromium levels were considerably lower than the control groups ($p<0.05$, Figure 2). In our study, copper and iron levels in bone tissue did not differ between groups (Figures 3 and 4).

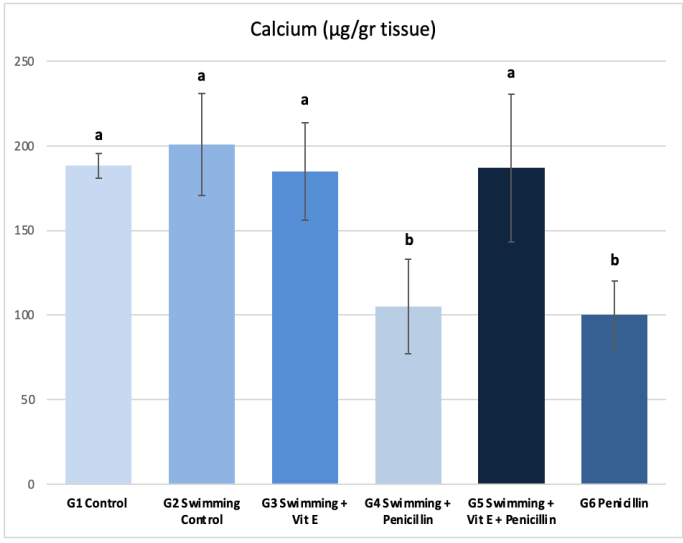

Figure 1. Calcium levels in bone tissue of study groups (µg/gr tissue) ($p<0.05$).

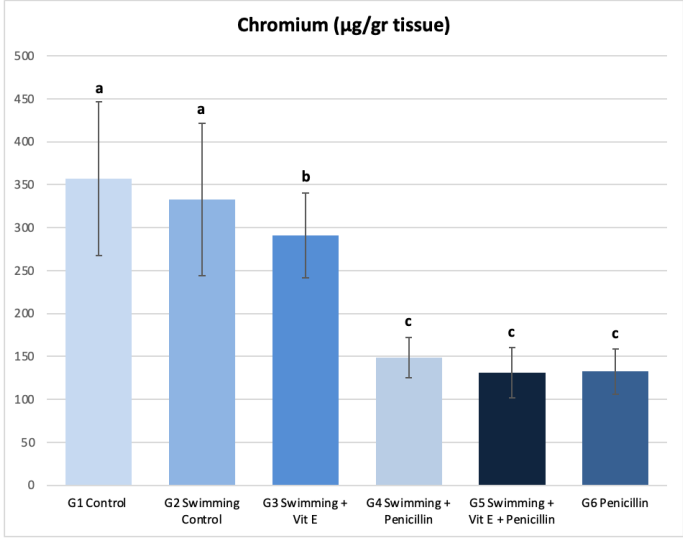

Figure 2. Chromium levels in bone tissue of study groups (µg/gr tissue) ($p<0.05$).

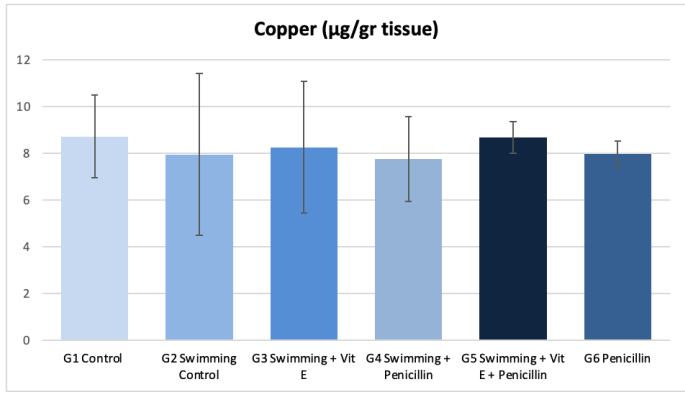

Figure 3. Copper levels in bone tissue of study groups (µg/gr tissue).

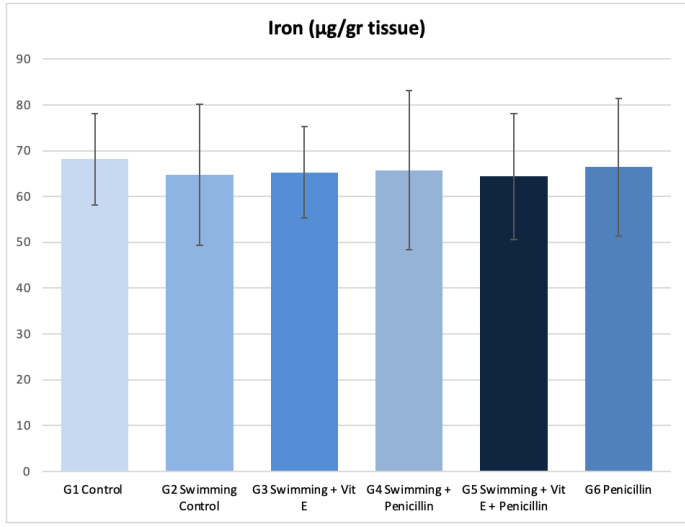

Figure 4. Iron levels in bone tissue of study groups (µg/gr tissue).

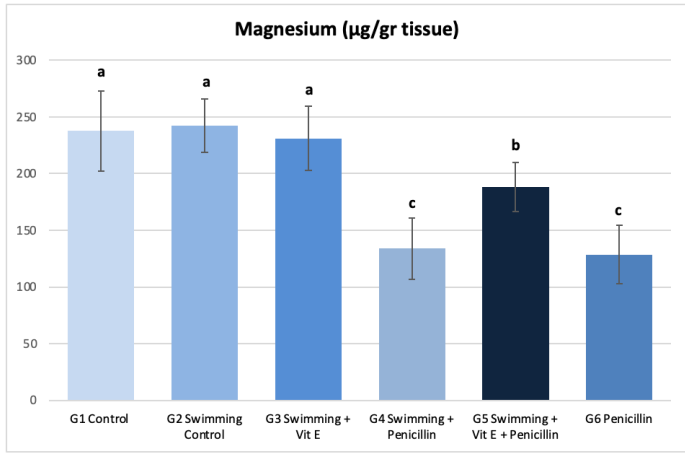

Figure 5. Magnesium levels in bone tissue of study groups (µg/gr tissue) ($p<0.05$).

The lowest bone magnesium and zinc values were obtained in the epileptic (G6) and epileptic swimming (G4) groups ($p<0.05$). Although vitamin E administration increased bone magnesium and zinc values in the epileptic swimming with vitamin E group (G5) compared to the epileptic (G6) and epileptic swimming (G4) groups ($p<0.05$), it did not reach the control values (Figures 5 and 6). Manganese and lead values in bone tissue did not differ between groups (Figures 7 and 8).

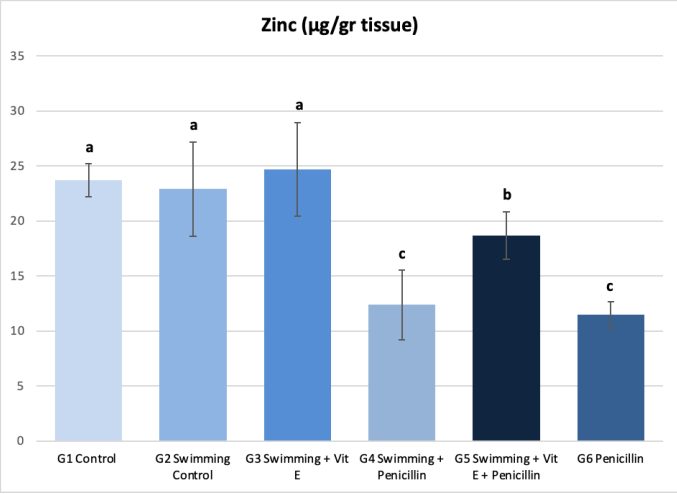

Figure 6. Zinc levels in bone tissue of study groups (µg/gr tissue) ($p<0.05$).

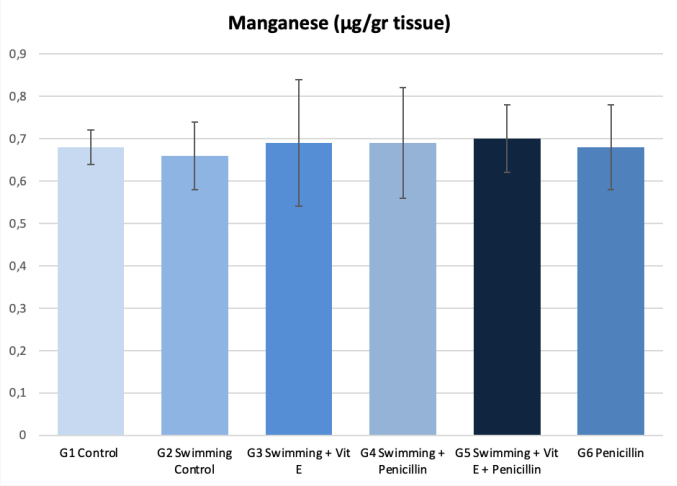

Figure 7. Manganese levels in bone tissue of study groups (µg/gr tissue).

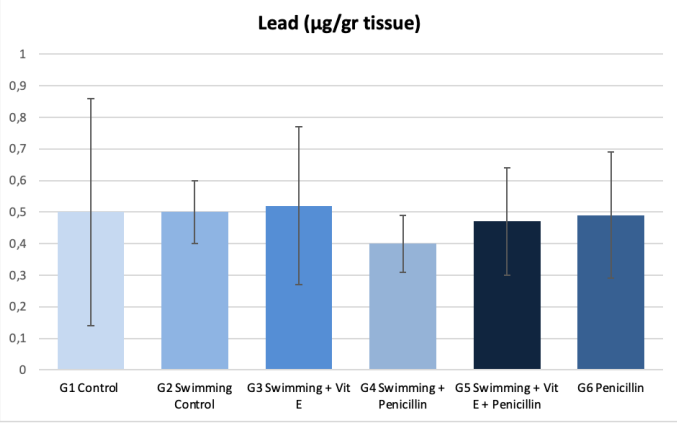

Figure 8. Lead levels in bone tissue of study groups (µg/gr tissue).

DISCUSSION

Epileptic patients are at a higher risk of fracture. Seizure activity, injuries due to falling, decreased bone strength, and adverse effects of antiepileptic drugs contribute to this increased fracture risk (16). It has been observed that deficiencies in vitamin D or disorders in vitamin D metabolism can have a negative impact on bone metabolism (16). Therefore, there is a growing interest in identifying potential bone element disorders in individuals with epilepsy and developing strategies to prevent disorders in bone metabolism (13).

In our study, the groups with the lowest bone calcium values were the epileptic (G6) and epileptic swimming (G4) groups. This suggests that chronic swimming exercise alone did not effectively restore the decreased bone calcium levels in epileptic rats. However, in the epileptic swimming group with vitamin E supplementation (G5), we observed an increase in bone calcium levels, reaching values similar to the control group. No studies investigating vitamin E and calcium-bone metabolism together in epileptic patients were found in our med-line scanning. The decreased levels of calcium observed in the bone tissue of the epileptic (G6) and epileptic swimming (G4) groups in our study may represent the first report on this specific subject. More importantly, our study demonstrates that vitamin E administration effectively increases bone calcium levels in the epileptic swimming group with vitamin E (G5) to those observed in the control group. This finding shows that suppressed bone calcium levels in epilepsy can be maintained with vitamin E supplementation.

It has been shown that vitamin E deficiency causes a decrease in bone calcium content in female rats (17). Vitamin E deficiency impairs bone calcium homeostasis with secondary hyperparathyroidism and vertebral bone loss (18). In contrast, administration of vitamin E compounds to rats with vitamin E deficiency reverses the decrease in bone calcium (17). The most important reason underlying the negative effects of vitamin E deficiency on bone-calcium metabolism is the suppression of calcium absorption from the digestive system as a result of the inhibition of the conversion of vitamin D to active metabolites in vitamin E deficiency (19). It has been reported that gastrointestinal disorders and loss of bone mass occur as a result of the inability of patients to adequately take some micronutrients such as vitamin E in various neurological diseases, including epilepsy (19). The findings of the studies presented above highlight a critical relationship between vitamin E and calcium-bone metabolism, independent of epilepsy. In our study, the observation that vitamin E supplementation effectively maintained suppressed bone calcium levels in epileptic rats is highly consistent with the findings reported by the aforementioned researchers.

The emergence of a significant suppression in bone chromium levels in patients receiving long-term parenteral nutrition therapy compared to the control group indicates the relationship between chromium and bone metabolism (20). Another study suggests that chromium supplementation in slaughter animals may affect bone metabolism by increasing the activity of insulin hormone (21). In our study, we found significantly lower bone chromium levels in all epilepsy groups (G4, 5, and 6) compared to the control groups. We could not find any previous research exploring the impact of chronic swimming exercise and vitamin E administration on chromium levels in bone tissue in epileptic patients. However, Wojciak et al. (22) reported a significant decrease in serum chromium levels in epileptic patients. Another study reported lower serum chromium levels in dogs with idiopathic epilepsy compared to control animals (23). The results of the reports presented above suggest that epilepsy may lead to changes in serum chromium levels. In our study, bone chromium levels were significantly suppressed in all epileptic rats. This finding represents the first report of decreased bone chromium levels in epileptic rats.

Magnesium is an essential mineral that shares similar chemical properties with calcium, which is considered an essential factor in bone health (24). Adequate dietary magnesium intake has been shown to be protective against osteoporosis (25). Due to the beneficial effect of magnesium on osteogenesis, magnesium-containing biomaterials are considered as potential agents for bone regeneration (24). In the current study,

the epileptic (G6) and epileptic swimming (G4) groups exhibited the lowest levels of magnesium and zinc in bone tissue. Although vitamin E administration in the epileptic swimming group with vitamin E (G5) led to an increase in bone magnesium and zinc levels compared to the epileptic (G6) and epileptic swimming (G4) groups, it did not reach the levels observed in the control group.

Magnesium, which participates in the pathogenetic processes of various neurological disorders, has also been associated with epilepsy (26). Attention has been drawn to the increased risk of epilepsy in parallel with already decreased blood magnesium levels (27). In addition, a long-term follow-up study covering a 22-year period showed that oral magnesium supplementation may reduce the risk of epilepsy (28). Similarly, Hamed et al. (29) reported that antiepileptic drugs may lead to bone destruction by disrupting mineral metabolism, including magnesium. The findings of our study, which revealed decreased bone magnesium levels in the epileptic (G6) and epileptic swimming (G4) groups, align with the previously reported studies. An important distinction of our study is that we measured magnesium levels in bone tissue rather than in blood fluid. In this respect, the findings of our study may be the first report on low bone magnesium levels in an epileptic rat model. Interestingly, our study revealed that vitamin E supplementation resulted in increased bone magnesium values in the epileptic swimming group with vitamin E (G5), compared to the epileptic (G6) and epileptic swimming (G4) groups. However, this increase did not reach the values of the control groups. Nevertheless, this finding suggests that vitamin E supplementation has the potential to partially correct the disrupted bone element metabolism associated with epilepsy.

Low zinc levels have been reported in epileptic patients (30,31). Since the N-methyl-D-aspartate receptor, which may play an important role in inducing epileptic discharges, is activated in zinc deficiency, low zinc levels have been observed in epileptic seizures (32). Based on this point, it is predicted that zinc supplementation can be used in the treatment of epilepsy (29). As a result, there is a proven relationship between epilepsy and zinc.

In our study, the lowest bone zinc values were obtained in epileptic (G6) and epileptic swimming (G4) groups. Although vitamin E administration could not reach the control values in the epileptic swimming with vitamin E group (G5), it increased the bone zinc levels significantly compared to the epileptic (G6) and epileptic swimming (G4) groups. Zinc, an essential element for bone metabolism, has an activity that can prevent osteoporosis under different pathological conditions (33). Zinc transport to bone tissue is also critical for bone physiology and metabolism (33). It is known that especially the addition of zinc to the diet significantly increases bone mineral density (33). Despite the known effects of zinc on bone and calcium metabolism, there is a lack of research specifically investigating the relationship between epilepsy, bone metabolism, and zinc levels. Likewise, we could not find any study on how vitamin E supplementation affects bone zinc levels in epilepsy.

A critical finding of our study is the significant increase in bone zinc levels observed in the epileptic swimming group with vitamin E (G5) compared to the epileptic (G6) and epileptic swimming (G4) groups. This finding suggests that the combined supplementation of vitamin E and zinc may play a crucial role in correcting impaired bone metabolism in individuals with epilepsy. Investigation of the relationship between zinc and bone metabolism in epileptic patients may provide us with new information.

Patients with epilepsy are known to have a high risk of fracture and a decrease in bone mineral density. In addition to the use of antiepileptic drugs, seizure-related falls and factors arising from the seizures themselves contribute to the increased risk of fractures in patients with epilepsy (34). Garip Ustaoglu et al. (35) showed that seizures occurring in rats in an experimental epilepsy model may lead to disorders in bone metabolism independent of antiepileptic drugs. In the present study, the observed changes in bone element metabolism in the epileptic rat model are consistent with previous findings reported by researchers.

Beneficial effects of physical activity have been reported in epileptic patients, as indicated by previous studies (9,10). However, in our study, chronic swimming exercise did not reverse the changes in bone element metabolism observed in the epileptic rat model. We could not find any studies investigating the relationship between epilepsy, bone element metabolism, and chronic exercise in med-line scans. However, vitamin E supplementation had a corrective effect on the deteriorated bone element metabolism in the epileptic rat model.

The findings of our study indicate that vitamin E supplementation improves calcium, magnesium, and zinc metabolism in the impaired bone tissue of the epileptic rat model.

When the findings of our study are examined as a whole;

1. Epilepsy causes changes in bone element metabolism.
2. Chronic swimming exercise does not significantly affect impaired bone element metabolism in the epileptic rat model.
3. Vitamin E supplementation reverses the deteriorated calcium, magnesium, and zinc levels in bone tissue in rats with epilepsy who underwent chronic swimming exercise.
4. This is the first research to investigate the link between epilepsy, bone element metabolism, and vitamin E supplementation.

Ethics Committee Approval: The study protocol was approved by the Ondokuz Mayıs University Animal Experiments Local Ethics Committeer (decision no. 2010-36). This research was performed on animals (rat).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- MA, EA, AKB, ET; Design- ET, GA, SBB; Supervision- MA, EA, AKB; Resource- ET, MA, EA; Materials- SBB, RM, AKB; Data Collection and/or Processing- RM, AKB; Analysis and/or Interpretation- MA, EA, RM, AKB; Literature Search- SBB; Writing- SBB; Critical Reviews- ET, MA, EA, RM, AKB.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: None.

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