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Metabolic Disorders That May Occur in The Immobilization Process of Organisms in Earthquake

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ketosis

Abstract: Deadly earthquakes have become a frequent event in the world and in our country. Therefore, it is a study conducted to understand the factors associated with hospitalized death during and after the earthquake, to reduce the mortality rate in patients hospitalized after the earthquake, and to help reduce chronic diseases and metabolic disorders. To date, different factors related to inpatient deaths in earthquakes have been discussed. In this study, Pub Med, Web of Science, Medline, Cochrane Library, Google Scholar, Google Academy and ULAKBİM electronic databases" earthquake" "immobilization" "exercise and pH balance", "acidosis", "ketosis" " immobilization" "oxidative stress" and other keywords. The titles and abstracts of all related articles reached by electronic scanning were reviewed. From the studies that were decided to be suitable for the subject, experimental studies, meta-analysis studies, systematic reviews and books written by reading the full text of the experimental studies were examined to create a comprehensive integrity on the subject.

Depremde Organizmaların Hareketsizlik Sürecinde Ortaya Çıkabilecek Metabolik Bozukluklar

Anahtar Kelimeler:
Deprem,
hareketsizlik,
oksidatif stres,
egzersiz ve pH dengesi,
asidoz,
ketozis

Özet: Ölümcül depremler dünyada ve ülkemizde sıkça karşılaşılan bir olay haline gelmiştir. Dolayısıyla deprem sırasında ve sonrasında hastanede yatan ölümlerle ilişkili faktörleri anlamak, deprem sonrası hastaneye yatan hastalarda ölüm oranını azaltmak, kronik hastalıkların ve metabolik bozuklukların azaltılmasına yardımcı olmak amacıyla yapılan bir çalışmadır. Bugüne kadar depremde yatan hasta ölümleriyle ilgili farklı faktörler tartışılmıştır. Bu çalışmada Pub Med, Web of Science, Medline, Cochrane Library, Google Scholar, Google Academy ve ULAKBİM elektronik veri tabanları "deprem" "immobilizasyon" "egzersiz ve pH dengesi", "asidoz", "ketozis" "immobilizasyon" "oksidatif" stres" ve diğer anahtar kelimeler. Elektronik tarama ile ulaşılan ilgili tüm makalelerin başlıkları ve özetleri incelenmiştir. Konuya uygun olduğuna karar verilen çalışmalardan deneysel çalışmalar, meta-analiz çalışmaları, sistematik incelemeler ve deneysel çalışmaların tam metni okunarak yazılan kitaplar incelenerek konu hakkında kapsamlı bir bütünlük oluşturulmuştur.

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1. INTRODUCTION

Meeting the physiological needs of organisms can be achieved by maintaining structural and metabolic balances. This depends on the creation of suitable conditions for the regulation systems of organisms. This state of balance is called homeostasis. The preservation of homeostasis is possible by eliminating the negative factors of endogenous or exogenous origin (Chaudhry et al., 2020). A malfunction that may occur in any of these balances causes deterioration of homeostasis. Along with the earthquake, the organism is faced with a series of problems starting from exposure to electromagnetic waves, ranging from fear, anxiety, thirst, not being able to feed, limited range of motion, water loss, and respiratory failure. This leaves the organism with many metabolic disorders as a result of the deterioration of hemostasis. Considering the role that skeletal muscles make up about 40% of human body weight and play in metabolic homeostasis, it has been revealed that a decrease in muscle mass, which is responsible for the uptake of 80% of resting blood glucose into the cell, will be responsible for many metabolic disorders (Pedreañez et al., 2011). While physical activity is defined as body movements in which energy consumption exceeds the basal level by contraction of skeletal muscles; Physical inactivity is defined as performing physical activity at levels lower than necessary to maintain health or prevent premature death (Booth et al., 2012). Lack or absence of physical activity causes damage to the neuromuscular junction, muscle denervation and a decrease in muscle mass (sarcopenia) (Mosole et al., 2014).

In this review study, the ability of the organism to perform its normal duties during an earthquake; Scientific texts and books on the metabolic disorders that may occur as a result of meeting the physiological minimum needs were examined. Pub Med, Web of Science, Medline, Cochrane Library, Google Scholar, Google Academy and ULAKBİM electronic databases" earthquake" "crush syndrome" "exercise and pH imbalances", "acidosis and exercise", "Chronic immobilization" "oxidative stress" Searched using "acute kidney injury" and other keywords. The titles and abstracts of all related articles reached by electronic scanning were reviewed. From the studies that were decided to be suitable for the subject, experimental studies, meta-analysis studies, systematic reviews and books written by reading the full text of the experimental studies were examined to create a comprehensive integrity on the subject.

1.1. Causes of Metabolic Disorders in Long-Term Drops

1.1.1. Immobilization

Immobilization can be defined as possible uncomfortable and prolonged immobility. In this situation, which lasts for a long time, the main task is to produce force and provide movement, as well as the inability of the skeletal muscles, which play an important role in glycemic control, regulation of metabolic genes, and protection of metabolic homeostasis in the organism. Skeletal muscles become even more important because of the mutual communication with other organs through the myokines they secrete (Pedersen, 2013). Conditions in which contractile activity is reduced or eliminated, such as immobilization or in a broader sense, cause a structural and functional deterioration in skeletal muscles by negatively affecting the balance between protein production and destruction in the muscle cell. This results in skeletal muscle atrophy, which is characterized by a concrete reduction in mass and a reduction in muscle strength and endurance (Kandarian and Jackman, 2006; Malavaki et al., 2015). Thus, the resulting muscle loss affects a certain muscle group due to the immobilization of a single extremity for a certain period of time after bone fractures or similar serious injuries (Chen et al., 2007). In the atrophy process that occurs due to disuse in skeletal muscle, the main losses in muscle proteins occur in myofibrillar proteins, which make up 60% of the muscle cell and are responsible for contraction. All these changes result in regression in muscle strength and endurance or the development of many chronic diseases, resulting in a decrease in quality of life (Batt et al., 2013).

Immobilization causes cartilage cell necrosis and reduction in total glucosaminoglycan mass, resulting in cartilage atrophy. As this situation causes softening in the cartilage tissue, the biomechanical durability of the cartilage decreases. It has been shown that the cartilage tissue atrophy and softening caused by immobilization do not completely improve upon return to mobilization (Haapala, et al., 1999). There are multiple metabolic disorders caused by immobilization. One of them is the disorders that occur as a result of the formation of reactive oxygen species (ROS).

1.2. Oxidative Stress Due to Immobilization

ROS emerges as a natural result of cellular activities in all compartments of the cell, especially mitochondria, cytoplasm, and endoplasmic reticulum (Gomez-Cabrera et al., 2020). Immobilization causes an increase in ROS production by three different mechanisms including xanthine oxidase, NADPH oxidase (NO_X) and mitochondria (Whidden et al., 2009). It has been reported that mitochondria are responsible for most of the increased ROS in the cell during the immobilization process. H_2O_2 released from mitochondria increased by 100% in the plantaris and soleus muscles of rats immobilized by casting for 14 days (Min et al., 2011). Although the mechanism responsible for the increase in ROS in mitochondria during the immobilization process is not fully elucidated, it has been stated that mitochondrial dysfunction triggered by the deterioration in Ca^{+2} homeostasis may be one of the mechanisms that may cause the increase in ROS. The increase in Ca^{+2} concentration in the cytoplasm due to immobilization leads to Ca^{+2} influx into mitochondria and mitochondrial depolarization (Bertero et al., 2020). Ca^{+2} activates the citric acid cycle activity and ROS-producing enzymes such as α-ketoglutarate dehydrogenase (Tretter et al., 2007). Immobilization causes an increase in ROS production by three different mechanisms including xanthine oxidase, NADPH oxidase (NOX) and mitochondria (Min et al., 2011). Xanthine oxidase, on the other hand, is oxidized by xanthine oxidase, which is formed by the metabolization of adenine and guanine under conditions of increased oxidative stress such as immobilization, causing the release of superoxide radicals in the extracellular space (Gomez-Cabrera et al., 2015). The increase in xanthine oxidase enzyme activity is considered a marker of oxidative stress. Studies in animal skeletal muscle using unloading and mechanical ventilation models by tail

suspension have shown that xanthine oxidase enzyme activity is increased in skeletal muscle fibers (Whidden et al., 2010). Inhibition of xanthine oxidase with pharmacological agents such as oxypurinol and allopurinol reduced muscle atrophy caused by immobilization and preserved contractile functions (Heinonen, 1996). Another enzyme, NADPH oxidase, is a mechanism responsible for the production of ROS in skeletal muscles and is a family of NOX enzymes. NOX, which is active in the transverse tubule, mitochondria, sarcolemma and sarcoplasmic reticulum, produces $O_2^{\cdot-}$ radicals by reducing molecular oxygen. It is known that NOX activity increases during the immobilization process (Gomez-Cabrera et al., 2020; Pamplona et al., 2008). Movement restriction stress causes oxidant damage as a result of dyslipidemia, disturbance in carbohydrate metabolism, decrease in nitric oxide (NO) production, atherosclerosis and imbalance in antioxidant status. Exposure to chronic stress is expected to increase lipid peroxidation by increasing oxidative stress, increase protein glycation with high blood sugar levels, and ultimately increase Advanced Glycation Endproducts (AGE) and advanced lipoxidation end product (ALE) levels. In recent years, oxidative stress has been considered as one of the main factors in the development of cardiovascular diseases (Dollery et al., 1997). Oxidation of LDL-cholesterol by ROS plays a role in the development of atherosclerosis (Güven et al.,2005). After six weeks of immobilization in mice, NOX enzyme activity, O_2^- production and lipid peroxidation were increased in the endothelium, endothelial functions were impaired and atherosclerotic lesions developed (Peyroux and Sternberg, 2006). In another study, increased oxidative stress as a result of immobilization in rats caused systolic hypertension and endothelial dysfunction (Rahbar, 2005).

However, it is emphasized that oxidative stress may be a factor that inhibits insulin signaling due to reduced physical activity and deterioration of redox homeostasis (Kessler and Sonnega, 1995). Phosphorylation of the serine amino acid in the structure of insulin receptor substrate 1/2 (IRS-1/2) by oxidative stress causes 17 IRS-1/2 to degrade and inhibits tyrosine phosphorylation and suppresses insulin signaling (Gulati et al., 2009). Oxidative stress triggers DNA damage, mutations and cancer development during replication (Bonfiglio et al., 2011). The 8-OH-dG products released as a result of the $OH^{\cdot}$ radical oxidizing the guanine base may pair with the adenine base during replication, leading to mutations. Under normal conditions, the antioxidant system and ROS production are in balance. However, the increase in ROS levels during the immobilization process disrupts this balance, and in response to this situation, the activities of some antioxidant enzymes change (Gomez-Cabrera et al., 2020). Investigating the level of oxidative stress in the skeletal muscle during immobilization. They showed that GSH was oxidized to GSSG under oxidative stress conditions and its concentration in the cell decreased by 34%. On the other hand, TBARS) increased 37% in the soleus muscle, which is a slow oxidative muscle, in the immobilization model created by casting compared to the control group (Kondo et al., 1993). Similarly, the increase in 4-HNE levels in the soleus muscles of mice immobilized by plastering for fourteen days indicates oxidative damage during the immobilization process (Min et al., 2011). Increasing ROS in the immobilization process oxidizes proteins, causing folding errors in the synthesis process, deterioration of their chemical structures and functional losses. The reactions of ROS with proteins, catalyzed by metals such as Fe^{2+}, and Cu^{2+}, result in the conversion of amino acids forming the protein structure into carbonyl derivatives (Stadtman et al., 1991). In another study, which was developed as a plaster-like method, in which both legs were immobilized with a stabilizing apparatus for fourteen days, it was shown that protein carbonyl and TBARS levels increased and GSH levels decreased in the immobilization group in the soleus and gastrocnemius muscle. The first study on the increase in free radical production during skeletal muscle contraction is another study by Davies et al. The disuse atrophy model applied in studies on whether oxidant stress plays a role in skeletal muscle atrophy due to disuse and the fact that different results have been obtained depending on which animal species this model performs makes it difficult to fully reveal the cause-effect relationship (Pellegrino et al., 2005). The fact that free radicals are also an important signaling molecule plays a role in this difficulty.

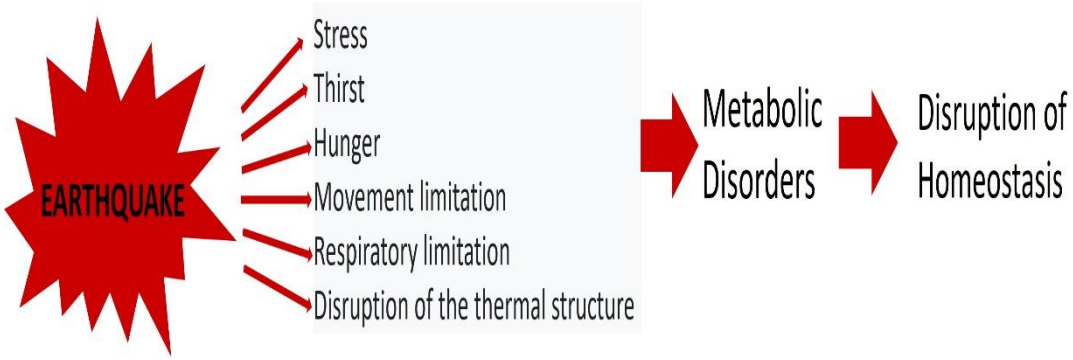

Figure 1. Metabolic disorders that may occur in the immobilization process of organisms in earthquake.

There are many studies showing that free radical production and oxidative damage increase in inactive muscles, increasing oxidative stress in skeletal muscle under disuse conditions, protein synthesis and It has been suggested that atrophy, which develops due to the deterioration of the balance between degradation is the main mechanism underlying the atrophy (Powers et al., 2011; Powers et al., 2012). There is an increase in free radicals and a decrease in antioxidant defense in the tail suspension model, where the load acting on the skeletal muscle is reduced by immobilization (In addition, ketones are converted to glucose by gluconeogenesis in the liver. When the hunger is prolonged, protein breakdown occurs in the muscles and alanine is also converted into glucose by gluconeogenesis in the liver. In other words, as the brain uses keto acids more and more, eliminating the need for glucose, the body adapts to prolonged fasting by conserving nitrogen. This change in fuel use reduces the need to mobilize amino acids from muscle for gluconeogenesis. Urinary nitrogen loss is initially in the form of urea when hepatic gluconeogenesis predominates, and then in the form of ammonia, reflecting increased glutamine uptake by the kidney. The carbon skeleton of glutamine is used for glucose production and replenishment of consumed HCO^{-}_{3}. The replacement of urea with NH_4^+ provides the osmoles necessary for urine flow and waste product excretion. Over time, urinary nitrogen loss is minimized as renal uptake of filtered ketone bodies becomes more complete. Adjustments in urinary Na^+ serve to minimize renal K^+ wastage and, together with changes in urine pH, minimize the possibility of uric acid precipitation., to rats exposed to mechanical ventilation in this study, they suggested that the main reason for the decrease in atrophy and contractile function in this model was oxidative stress (Whidden et al., 2010). Protein carbonyl levels in muscle biopsy samples taken on the eighth and thirty-fifth days of prolonged bed rest, which is one of the human abstinence models, were investigated by oxyblot analysis. Accordingly, while bed rest on the eighth day did not cause a decrease in the muscle fiber cross-sectional area or a change in protein carbonyl levels, at the end of the thirty-fifth day, in biopsy samples taken from the vastus lateralis muscle, there was an 18% decrease in the cross-sectional area of the muscle fibers and protein carbonyl, which is an indicator of oxidative stress. levels were also increased (Dalla et al., 1995). Immobilization and restraint stress have been associated with increased Blood–Brain Barrier (BBB) permeability in the hypothalamus, midbrain reticular formation, and the cerebellum (Malabe and Stonestreet, 2007). On the other hand, a seven-day confined cage application resulted in a 17.2% loss in rat soleus muscle weight/body weight ratio, while no increase in protein carbonyl levels was detected. All these findings indicate that protein oxidation is observed in disuse conditions induced by the seven-day habitat-limited cage application. Preservation of skeletal muscle mass is possible by balancing protein synthesis and protein breakdown rate. Even a decrease in protein synthesis (Huertas et al., 1992) and/or a minimal increase in protein breakdown rate (Koesterer et al., 2002) results in significant muscle atrophy. However, although a decrease in protein synthesis rate is observed in skeletal muscle atrophy, the determining factor is the increase in protein degradation rate (Furuno et al., 1995). A decrease in the amount of glutathione is an indirect indicator of oxidative stress. Kondo et al. (Kondo et al., 1993) reported a decrease in the amount of GSH in the atrophied group with the single-leg immobilization method. Similar results have been demonstrated in denervation atrophy and studies in which rats were not allowed to move at all. Especially high-stress rates are observed in animals according to atrophy methods. This stress causes serious decreases in the amount of GSH (Demiryürek et al., 2004). Under immobilization conditions, oxidative stress, which cannot be controlled due to increased ROS production and suppression of the antioxidant defense system, causes damage to important structures in cells and loss of function. It is stated that in cases of increased oxidative stress, doxycycline will be protective against oxidative damage and protein glycation in rats exposed to movement restriction stress (Dirks et al., 2016). In addition, there are studies expressing that kefir and yogurt are used as a metabolism regulator and tissue repairers due to their antioxidative properties in many tissue degenerations (Güven 2005; Güven et al., 2020). In addition, it has been reported that cognitive functions regress as a result of oxidative damage of macromolecules due to immobilization, while even a single session of exercise after immobilization provides the return of cognitive functions to normal by eliminating macromolecule damage (Saretzki et al., 2002). While these findings reveal the negative effects of oxidative stress on the increased risk of chronic diseases caused by immobilization, they also emphasize the importance of oxidative stress in the formation of pathologies and chronic diseases due to a sedentary lifestyle.

1.3. Acidosis

Under normal conditions, 10,000 to 20,000 mmol of carbonic acid and 80-120 mmol of metabolic acid are produced daily in the organism (Günay et al., 2018). Acids give hydrogen ions to solutions, while bases remove hydrogen ions by binding them. In other words, pH is defined as the negative logarithm of the hydrogen ion concentration in a solution and is expressed as $pH = - \log [H^+]$ (Widmaier et al., 2019). Maintaining H+ homeostasis in body fluids and cells, that is, maintaining the balance between the intake and production of hydrogen ions and their excretion, is very important for the body's acid-base balance (Paşaoğlu et al., 2019). However, metabolic acidosis occurs when the pH value in intracellular and extracellular fluids is not maintained due to many factors. Metabolic acidosis or alkalosis is the metabolic disorder seen in cases where the disturbances in the body's acid-base balance are caused by changes in the HCO^{-3} ion concentration, and as a result, changes in the pH level (Telci, 2011). This is common in earthquakes. As seen after the Marmara and Van earthquakes, the critical picture that draws attention to the change in the pH value of the intracellular and extracellular fluids when the conditions change, this picture in some patients who seem well under the debris or immediately after being rescued deteriorate rapidly, possibly due to severe metabolic acidosis that occurs during trauma and this condition. There are studies stating that acidosis causes hyperkalemia (Sever et al., 2011; Günay et al., 2018).

The occurrence of metabolic acidosis as a result of high anion gap and normal chloride level is defined as normochloremic metabolic acidosis, while the occurrence of

metabolic acidosis as a result of a normal anion gap and high chloride level is defined as hyperchloremic metabolic acidosis. There is usually an anion gap in metabolic acidosis, and the increase in components such as kidney failure, ketoacidosis, salicylate poisoning, and lactic acidosis, especially due to the change in organic acids and unmeasured anion concentrations, causes metabolic acidosis (Günay et al., 2018; Paşaoğlu et al., 2019).

1.4. Ketosis

Hunger is generally defined as the ingestion of little or no food in humans for periods of 12 hours to three weeks. During fasting, liver glycogen, which is the glucose storage polymer, is broken down into glucose by glycogenolysis, thus protecting blood glucose. Greater changes occur in the body as hunger prolongs and glycogen stores decrease. For example, storage triglycerides in adipose tissue are released into the circulation as glycerol and fatty acids (Rui, 2014; Cahill., 2006). Glycerol is converted to glucose in the liver and this process is called gluconeogenesis. Fatty acids are oxidized and used as a direct energy source in tissues such as liver and muscle. In addition, fatty acids pass from the white adipose tissue to the liver and are oxidized to acetyl-CoA in the liver. Then, β-hydroxybutyrate and Acetoacetate are formed from acetyl-CoA. These ketone bodies are released into the circulation to be used by the tissues (Palmer et al., 2015; Palmer .2021). Although the brain cannot use fatty acids as an energy source, it can use ketone bodies (Frise et al., 2013). approximately 70% of the energy used is met by ketones (Cahill., 2006).

In addition, ketones are converted to glucose by gluconeogenesis in the liver. When the hunger is prolonged, protein breakdown occurs in the muscles and alanine is also converted into glucose by gluconeogenesis in the liver. In other words, as the brain uses keto acids more and more, eliminating the need for glucose, the body adapts to prolonged fasting by conserving nitrogen. This change in fuel use reduces the need to mobilize amino acids from muscle for gluconeogenesis. Urinary nitrogen loss is initially in the form of urea when hepatic gluconeogenesis predominates, and then in the form of ammonia, reflecting increased glutamine uptake by the kidney. The carbon skeleton of glutamine is used for glucose production and replenishment of consumed HCO^{-}_{3}. The replacement of urea with NH_4^+ provides the osmoles necessary for urine flow and waste product excretion. Over time, urinary nitrogen loss is minimized as renal uptake of filtered ketone bodies becomes more complete. Adjustments in urinary Na^+ serve to minimize renal K^+ wastage and, together with changes in urine pH, minimize the possibility of uric acid precipitation (Palmer et al., 2015; Palmer .2021; Frise et al., 2013).

2. CONCLUSION

Since living organisms are exposed to electromagnetic waves, multiple problems arise in metabolism due to factors such as fear, anxiety, thirst, inability to feed, limitation of movement area (immobilization), water loss, respiratory failure. As a result of the deterioration of hemostasis in this organism, it faces many metabolic disorders.

The uncomfortable and long-lasting main task under the dent is to generate force, and while the communication with other organs through myokines secreted by the skeletal muscles that undertake the movement decreases, the conditions in which the contractile activity decreases or disappears disrupts the balance between protein production and destruction in the muscle cell. The increase in the concentration of Ca^{+2} in the cytoplasm due to immobilization causes Ca^{+2} to flow into the mitochondria and mitochondrial depolarization, while it causes an increase in ROS production by three different mechanisms including xanthine oxidase, NADPH oxidase, (NOX) and mitochondria. Movement restriction stress causes oxidant damage as a result of dyslipidemia, disturbance in carbohydrate metabolism, decrease in nitric oxide (NO) production, atherosclerosis and imbalance in antioxidant status. The fact that exposure to chronic stress increases lipid peroxidation by increasing oxidative stress brings protein glycation with the high blood sugar levels it will cause. Precautions and treatments in the direction that all these changes may occur will increase the loss of life and the quality of life.

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