

ORIGINAL ARTICLE

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Investigation of the effects of ketogenic and western diet on tissues lipid peroxidation and antioxidant enzymes in rats with pressure ulcer**Songul Doganay¹, Serap Cetinkaya Ozdemir², Nurten Bahtiyar³,
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**Abstract**

It was aimed to investigate the effects of different diets on lipid peroxidation and some antioxidant enzymes in the liver, kidney, heart, and serum in rats with pressure ulcers. Thirty adult Sprague Dawley male rats were used. Rats were divided into three groups as standard diet group, ketogenic diet group, and western diet group. The dorsal skins of rats of all groups were squeezed between two neodymium magnetic cylinders while under anesthesia for creating ulcers. The rats were fed with tap water and a specially prepared ad libitum diet according to the determining diets. Malondialdehyde, Glutathione, and Catalase levels were measured by spectrophotometric methods in the liver, kidney, heart, and serum samples taken at the end of the experiment. Malondialdehyde levels in the serum, liver, and kidney decreased in the ketogenic diet group compared to the standard diet group and the western diet group; glutathione levels in the kidney were higher in the western diet group compared to the standard diet and the ketogenic diet groups, and in the heart, it significantly decreased in the standard diet group compared to the ketogenic diet and the western diet groups ($p < 0.05$). Catalase levels in the kidney were higher in the ketogenic diet group compared to the other two groups, and in the liver, it was higher in the standard diet group than the ketogenic diet and the western diet groups ($p < 0.05$). It is seen that feeding with a ketogenic diet reduces the damage caused by oxidative stress in tissues by decreasing lipid peroxidation and increasing antioxidant enzyme levels or keeping them unchanged.

Keywords: Ketogenic Diet; Nutrition; Oxidative Stress; Pressure Ulcer; Western Diet**Introduction**

Many studies have shown that damage to skin for various reasons (such as burns, pressure ulcers) produces reactive oxygen species, then initiates systemic inflammatory reactions and leads to lipid peroxidation [1-3]. Lipid peroxidation is caused by the deformation of cell membrane phospholipids by oxidizing radicals. It has been shown that there is an intense relationship between the amount of lipid peroxidation and tissue damage [1]. It is stated that the system which protects against oxidative damage is seriously impaired in patients with pressure sores. Depending on this situation, it was reported that the oxidative imbalance plays a role as a causal factor in the development of pressure sores.

In a study conducted on 100 adult patients with pressure sores and 213 healthy adults, it was determined that the individuals with pressure ulcers had higher oxidative stress than the healthy individuals [4]. In different studies, it was observed that the MDA levels, which are an indicator of the lipid peroxidation following the formation of pressure ulcers, increased and the GSH levels decreased significantly [5-7]. It was determined that there was a significant increase in the MDA levels of all internal organs in the group with pressure ulcers and this increase was more pronounced in the kidneys, stomach, and intestine, and that the tissue GSH levels decreased significantly and this decrease was more severe in the stomach and intestine [6-7]. Reactive oxygen species are consistently produced in low and measurable concentrations in cells and tissues under normal physiological conditions. Their concentrations are determined by the balance between the production and clearance rate of various antioxidant compounds and enzymes [2]. On the other hand, cells defend themselves against the potential damage of reactive oxygen species in cells through their antioxidant mechanisms, including various enzyme systems, some antioxidant molecules, vitamins, and trace elements. There

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is a strong balance between the production and destruction of the reactive oxygen species. If this balance is lost, reactive oxygen species are produced in excess and oxidative damage begins to occur in all tissues [8]. In other words, oxidative damage in a cell depends on two factors. First is the production of increased reactive oxygen species as a result of chronic diseases or exogenous sources; second is the reduction of antioxidant and enzymatic cofactors in the diet. Also, dietary compositions can affect both conditions [9].

Low-carbohydrate and high-fat ketogenic diets have been used primarily in childhood epilepsy treatment since the early 1920s and re-emerged as an important alternative clinical approach in the 1990s [10]. It has also been used therapeutically in the treatment of obesity, type 2 diabetes, and many other diseases [11, 12]. Western diets (WD) are rich in animal fats and food additives but deficient in other plant-derived molecules such as fiber, vitamins, minerals, and antioxidants [13]. Several recent experimental animal and clinical studies suggest that Western diet models directly or indirectly affect the immune system by increasing the markers of inflammation [14]. In male rats fed by a ketogenic diet, a high-sucrose and a high-fat western diet; the ketogenic diet increased glucose tolerance and insulin sensitivity compared to the western diet, and decreased de-novo lipogenesis in the liver [15]; while the western diet impaired fatty acid oxidation and increased Novo lipogenesis [16].

Today, the contribution of dietary practices to the treatment of various pathological conditions is drawing researcher's attention day by day. Therefore, the interest in diet studies is increasing. Despite the success of diet types in clinical and experimental studies on showing causes, few studies have been conducted point to the possible mechanisms of diets applied and their effects on different aspects of the metabolism in different systems and organs. This situation raises the question of "What kind of physiological changes do the dietary types applied cause on other tissues in the body?"

Considering all these impacts; no studies have been found in the literature applied to rats with pressure ulcers to compare the effects of the standard rat feed, ketogenic diet, and western diet on the oxidative stress and antioxidant enzymes involved in the antioxidant defense against the oxidative stress. Therefore, in this study, it was aimed to investigate the effects of three different diet types applied to rats with pressure ulcers to malondialdehyde (MDA) level which is an important indicator of increased lipid peroxidation in the oxidative stress, to glutathione and catalase (CAT) levels which are two antioxidant enzymes involved in antioxidant defense against the oxidative stress, in the liver, kidney, heart, and serum.

Material and Methods

Ethical considerations

Approval was obtained from Sakarya University Animal Care and Use Ethics Committee for the experimental protocols (approval date and number; 04.03.2020/22). All applications on animals were carried out in Sakarya University Animal Laboratory following international guidelines. Practices on rats were humanely, and the standards conformed to those of current ethical animal research practice.

Study design and creating groups

In this study, 30 Sprague-Dawley male rats weighing 110-185 grams, 10-12 weeks old, were used. Rats were kept in wire cages under standard laboratory conditions (12/12 hours light/dark-light cycle, temperature 22°C, humidity 50-60%) for 9 weeks. All rats were fed with tap water and ad libitum specially prepared according to the determining diets. Rats were randomly divided into 3 groups (standard diet, western diet, ketogenic diet) with 10 animals in each group.

Standard diet group; The rats in this group were fed a normal standard diet (77.3% of calories consisting of carbohydrates, 2.7% of fat, and 20% of protein) for 9 weeks.

Western diet group; The rats in this group were fed a Western diet (39.70% of calories consisting of carbohydrates, 39.51% of fat, 19.53% of proteins, and 1.26% of other components) for 9 weeks [17].

Ketogenic diet group; The rats in this group were fed a ketogenic diet (4.95% of calories consisting of carbohydrates, 74.24% of fats, 19.53% of proteins, and 1.28% of other components) for 9 weeks [18].

Pressure ulcer creation

In this study, the pressure ulcer rat model developed by Stadler et al. [19] was used. The animals were fed the specified diets for three weeks before creating the ulcer model. Anesthesia was administered in the 4th week of the experiment (Ketamine 100 mg/kg-Xylazine 10 mg/kg IM). Then the area between the two scapulae was shaved. The skin in this area was gently pulled and all dermal structures except muscles were clamped between 2 neodymium magnet cylinders (15x5 mm diameter, 2000 Gauss strength, 6.53 g weight). The compression procedure was applied in the form of magnet insertion for 8 hours and release for 8 hours (ischemia/reperfusion model), as prescribed in the literature, and pressure ulcers were created after 72 hours. The rats were kept in single cages throughout the experiment.

At the end of the experiment, animals were sacrificed with high-dose blood drawing under general anesthesia with 60 mg/kg (i.p.) ketamine and 8 mg/kg xylazine (i.p.) injection, and tissue samples were taken and stored at -80°C until laboratory analysis. Malondialdehyde, glutathione, and catalase levels were measured by spectrophotometric methods in the heart, kidney, liver homogenates, and serum samples taken for analysis.

Measurement of biochemical parameters

Preparation of tissue homogenates

Tissues were washed with 0.9% NaCl solution after weighing. After washing, they were centrifuged (+4 °C, 3000 RPM, 10 min). Then they were homogenized in cold 1.15% KCl, 0.01 M solution of sodium-potassium phosphate (pH=7.4). 10% tissue homogenates were prepared. These homogenates were centrifuged at 10.000g for 20 minutes, at + 4 °C. The supernatant was taken and used to determine the MDA, GSH, and CAT parameters in the tissues. Protein measurement of the samples was made using the Lowry method [20]. The determination of MDA was carried out

by Buege and Aust's [21] method. Results are given as nM/mg protein. GSH determination was carried out Beutler method [22]. Results are given as $\mu\text{M}/\text{mg}$ protein. CAT activity was determined by Beers [23]. Results are given as U/mg protein.

Data analysis

Statistical analysis was performed using SPSS 22.0 package program (SPSS Inc. and Lead Tech. Inc. Chicago, the USA). Shapiro Wilk test was used for the normal distribution of the data. One-way ANOVA and Kruskal Wallis test were used to compare more than two variables. TUKEY HSD test was used for the variables with homogenous significance variances within the group. The significance of the difference between the two groups was evaluated with the Mann-Whitney U test. The significance limit was accepted as $p < .05$.

Results

As a result of biochemical measurements, the malondialdehyde levels were found to be significantly different in the serum, liver, and kidney tissues. In comparisons between groups, the serum and the liver were found to be significantly lower in the ketogenic diet group compared to the standard diet group ($p = .009$, $p = .000$) (Figure 1). In the comparisons between groups in the kidney tissue, the malondialdehyde levels were statistically significantly lower in the ketogenic diet group compared to the standard diet and the western diet groups ($p = .023$, $p = .014$) (Figure 1).

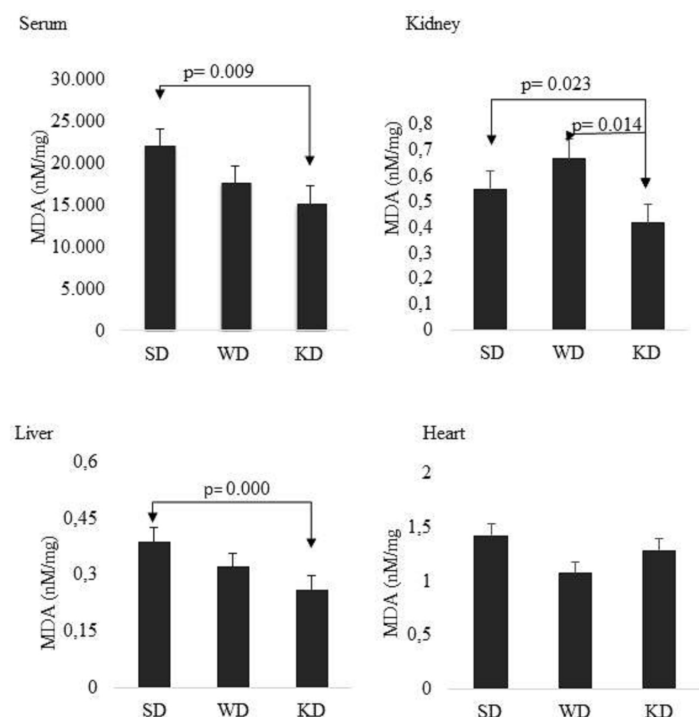


Figure 1. Effect of diets on MDA levels in tissues. MDA, malondialdehyde; SD, standard diet; KD, ketogenic diet; WD, western diet. Values are the mean $\pm$ SD. Significance level $p < 0.05$

When the glutathione levels were examined (Figure 2) while there were no differences between groups in the liver and serum ($p > .05$), it was observed that there were significant changes in the kidney and heart tissues. The kidney tissue was higher in the western diet group compared to the standard diet group, and low in the ketogenic diet group ($p = .016$, $p = .001$, respectively). The Glutathione levels

in the heart tissue were significantly higher in the ketogenic diet group compared to the standard diet group ($p = .008$)

When the catalase levels in the tissues were examined, there were no significant changes in serum (Figure 2) and heart tissue ($p > .05$). The Catalase levels of kidney tissue were found to be higher in the ketogenic diet group. In the comparison made to determine the group that made a significant difference, it was found that the catalase levels were significantly increased ($p = .001$) in the ketogenic diet group compared to the standard diet group. In the comparison of the liver tissue between groups, a significant increase was observed in the standard diet group compared to the ketogenic diet and the western diet groups ($p = .008$, $p = .000$, respectively), and in the ketogenic diet, the group compared to the western diet group ($p = .000$) (Figure 3).

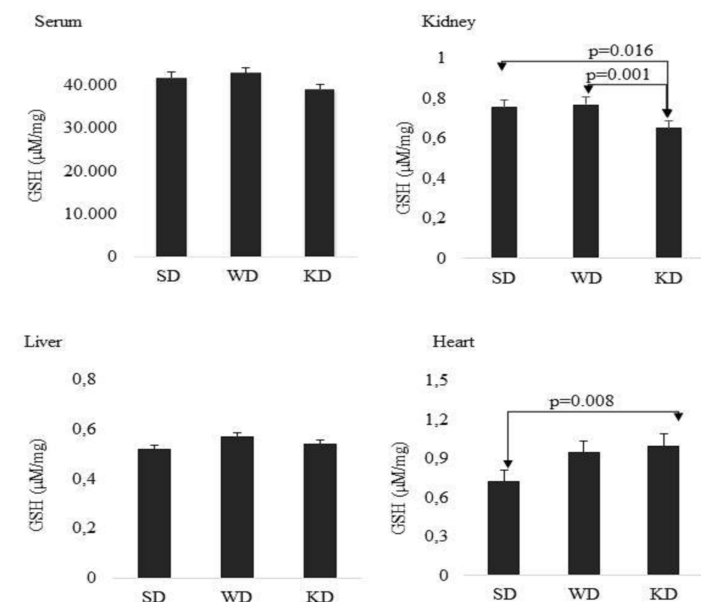


Figure 2. Effect of diets on GSH levels in tissues. GSH, glutathione; SD, standard diet; KD, ketogenic diet; WD, western diet. MDA, malondialdehyde; Values are the mean $\pm$ SD. Significance level $p < 0.05$

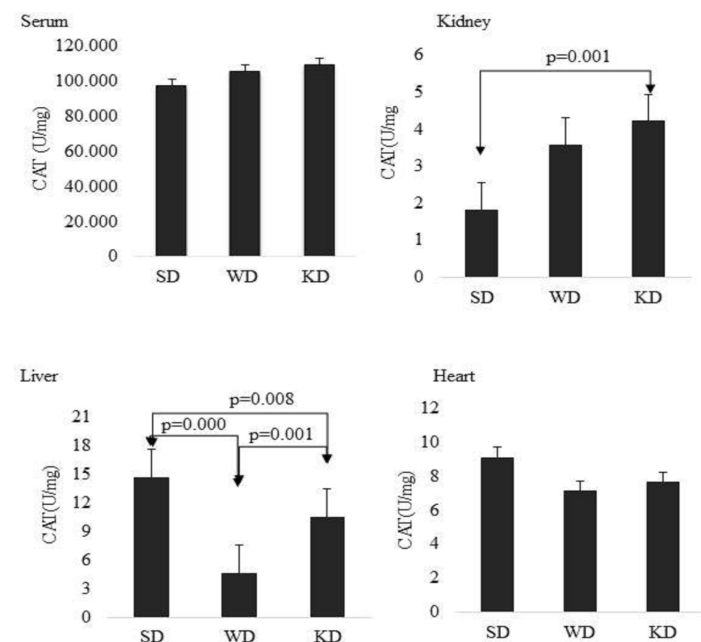


Figure 3. Effect of diets on CAT levels in tissues. CAT, catalase; SD, standard diet; KD, ketogenic diet; WD, western diet. Values are the mean $\pm$ SD. Significance level $p < 0.05$

Discussion

Differences in the diversity and concentrations of nutrients in the content of different diet types are thought to affect human health, especially the occurrence of chronic diseases, in different ways [24]. The purpose of regular and balanced nutrition in disease states is to assist medical treatment by providing adequate levels of energy, fluids, and nutrients to maintain homeostasis, strengthen and maintain immune system activity, reduce the risk of overnutrition, protein catabolism, and nitrogen loss [25]. Nurses must have information about diets. Because nurses responsible for health care should provide nutritional advice to patients to ensure their health management [26]. For this reason, in this study, the effects of different diet types on the oxidative stress and antioxidant enzymes in the serum, liver, kidney, and heart tissues were investigated in an experimentally created ulcer model in rats.

When an injury occurs as a result of tissue destruction, various complex and interrelated structuring processes begin in the organs/systems of the body [27]. In our study, the malondialdehyde levels in tissues were found to be significantly different in the serum, liver, and kidney tissues. In the serum and liver, the levels were statistically significantly lower in the ketogenic diet group compared to the standard diet group. Again, in the kidney tissue, the levels were significantly lower in the ketogenic diet group compared to the standard diet and the western diet groups. Malondialdehyde is the end product of lipid peroxidation and is an essential biochemical parameter used as an oxidative stress marker. Conflicting results have been reported in dietary studies in the literature. As in some studies [28-30], it is seen in our study that the ketogenic diet reduces the effects of oxidative stress and antioxidants. In a study, it has been shown that long-term feeding with a ketogenic diet (75% kcal Fat) regulates the glutathione biosynthesis in the hippocampus of male rats and increases the mitochondrial antioxidant capacity [31]. A different study reported that feeding with a ketogenic diet decreases GSSG (oxidized form of glutathione) in the liver and increases the GPx enzyme levels. In the same study, it was reported that feeding with a ketogenic diet decreased TNF α and CD11b inflammatory markers in the liver compared to feeding with a western diet [32]. Contrary to these studies, Allen et al [33]. Reported that there was an increase in protein oxidation and lipid peroxidation in the livers of rats that they created a ketosis model. This ketogenic diet increased oxidative stress. Again, Holland et al [34]. showed in their study that there was no improvement in oxidative stress markers in the liver or brain in rats fed with a ketogenic diet (67% kcal fat). These differences are thought to be likely due to the macronutrient composition used in the studies.

In the present study, there were no significant differences between the groups in glutathione levels in the liver and serum. However, it increased in the heart tissue in the ketogenic diet group compared to the standard diet and the western diet groups. This increase was statistically significant in the standard diet group. There were no significant changes in tissue catalase levels in the serum and heart tissues. While the kidney catalase levels increased in the ketogenic diet group compared to both groups fed with the standard diet and the western diet, this increase was statistically significant compared to the standard diet group. It was significantly higher in the standard diet group compared to the ketogenic diet and the

western diet groups, in the ketogenic diet group compared to the western diet group in liver tissues. It has been widely suggested that nutritious dietary ingredients may inhibit the development of various chronic diseases, often due to increased sensitivity to or protection against free radicals [28]. The oxidative stress is caused by either the overproduction of reactive oxygen species or an increase in the concentrations of active oxygen species as a result of the disruption of antioxidant defense systems. Ketogenic diets were developed in the 1920s to combat epileptic seizures. However, it has been shown that ketogenic diets are used in conditions other than epilepsy for various reasons including migraine, autism, depression, polycystic ovary syndrome, especially Type 2 diabetes mellitus and obesity, where glucose metabolism is impaired [35]. For example, short-term (4-6 weeks) and long-term (up to 12 months) studies have shown that ketogenic diets cause greater fat loss in obese individuals [36].

In studies investigating the effects of the western diet, it has been shown that the long-term consumption of western diets can negatively affect the homeostasis in the body by activating the immune system as well as weight gain, pathological changes in lipids, and physiopathological changes in the energy metabolism [37]. It has been shown that hepatic lipogenesis dysregulation is an important cause of heart failure in animals fed a high-fat western diet. Also, prolonged exposure of the heart to a large supply of fuel can have pathological consequences due to the formation of harmful glucose derivatives such as reactive oxygen species and protein glycosylation and lipid metabolism [38]. Excessive reactive oxygen species production affects a range of cellular events, including the mitochondrial structure, function, and metabolism [39]. In a study, the western diet was shown to affect both long and short-term memory by inducing oxidative stress in rats. In the results of this study, it was reported that while superoxide dismutase, catalase, and glutathione levels decreased in the hippocampus of rats, increased TBARS levels reduced hippocampal activity [40]. Although the physiological mechanisms of western diets on other organs including the brain are not well understood, both experimental and human studies have shown that obesity is associated with increased oxidative stress markers and lipid peroxidation [41]. It has been shown that consuming a meal of the western diet in morbidly obese individuals causes a significant decrease in plasma superoxide dismutase activity [42].

Conclusion

In conclusion, feeding with a very high-fat, low-carbohydrate ketogenic diet appears to prevent oxidative damage by reducing lipid peroxidation in tissues in any stressor situation, increasing antioxidant enzyme levels or keeping them stable, and reducing possible oxidant damage in tissues.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

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Ethical approval

Approval was obtained from Sakarya University Animal Care and Use Ethics Committee for the experimental protocols (approval date and number; 04.03.2020/22).

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