OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2024;9(4):322-328. *Online Türk Sağlık Bilimleri Dergisi 2024;9(4):322-328*

Comparison of the Effects of the Ketogenic Diet and Western Diet on the Retina in Rats with Diabetes

Diyabetik Ratlarda Ketojenik Diyet ve Western Diyetin Retina Üzerine Etkilerinin Karşılaştırılması

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ABSTRACT

Objective: This study aimed to investigate the effects of different diets on the retina in rats with diabetes mellitus (DM).

Materials and Methods: In our study, a total of 4 groups were formed: healthy and regular diet (Group 1), DM-induced and regular diet (Group 2), DM-induced and ketogenic diet (KD) (Group 3), DM-induced and western diet (WD) (Group 4). Tissue sections were histo-scored using Vascular endothelial growth factor (VEGF) and Caspase-3 immunohistochemical staining method. The thicknesses of the retinal layers stained with hematoxylin-eosin were compared.

Results: Retinal staining with VEGF revealed a greater incidence of low-intensity staining in Group 3 (p: 0.018). There was no notable disparity observed across the groups in the staining of the retinas with Caspase-3 (p: 0.65). When the thicknesses of the retinal layers were compared, it was observed that the inner-outer nuclear, inner plexiform and ganglion layers were significantly thicker in the WD group than the other groups (p values <0.001, 0.013, 0.006, 0.017, respectively). There was no significant difference between the groups regarding choroidal thickness (p: 0.118).

Conclusions: The KD can be considered advantageous or less detrimental compared to the WD. Nevertheless, while the ketogenic diet has shown beneficial outcomes in the short term, its long-term impact remains uncertain.

Keywords: Caspase-3, diabetic retinopathy, ketogenic diet, VEGF, western diet

ÖZ

Amaç: Bu çalışmanın amacı, DM oluşturulmuş ratlarda farklı beslenme tarzlarının retina üzerindeki etkilerini araştırmak.

Materyal ve Metot: Çalışmamızda sağlıklı ve normal beslenme uygulanmış (Grup 1), DM oluşturularak normal beslenme uygulanmış (Grup 2), DM oluşturularak KD uygulanmış (Grup 3), DM oluşturularak WD uygulanmış (Grup 4) olmak üzere toplam 4 grup oluşturuldu. Doku kesitlerinden VEGF ve Caspase-3 immünohistokimyasal boyama yöntemi kullanılarak histoskorlama yapıldı. Hematoksilen-eozin ile boyanan retina tabakalarının kalınlıkları karşılaştırıldı.

Bulgular: Retinaların VEGF ile boyanmasında Grup 3'te az yoğun boyanma daha yüksek oranda bulundu (p: 0.018). Caspase-3 ile retinaların boyanmasında gruplar arasında anlamlı fark görülmedi (p: 0.65). Retina tabakalarının kalınlıkları karşılaştırıldığında; iç nükleer, iç pleksiform, dış nükleer ve ganglion tabakalarının Grup 4'te diğer gruplardan anlamlı olarak kalın olduğu görüldü (Sırasıyla p değerleri <0.001, 0.013, 0.006, 0.017). Koroid kalınlıkları açısından gruplar arasında anlamlı fark görülmedi (p: 0.118).

Sonuç: Ketojenik diyetin western tipi diyete göre faydalı veya daha az zararlı olduğu söylenebilir. Ancak ketojenik diyetle ilgili kısa vadede olumlu sonuçlar bildirilmesine karşın uzun vadede etkisi bilinmemektedir.

Anahtar Kelimeler: Caspase-3, diyabetik retinopati, ketojenik diyet, VEGF, western diyet

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Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 18/06/2024
Kabul Tarihi/ Accepted: 06/12/2024
Online Yayın Tarihi/ Published: 25/12/2024

Atıf / Cited: Sönmezoğlu Hİ and et al. Comparison of the Effects of the Ketogenic Diet and Western Diet on the Retina in Rats with Diabetes. *Online Türk Sağlık Bilimleri Dergisi* 2024;9(4):322-328. doi: 10.26453/otjhs.1502084

INTRODUCTION

Diabetic retinopathy (DRP) is a prevalent and specific microvascular complication of DM, recognized as the leading cause of preventable blindness among working-aged individuals globally.[1,2] The pathophysiology of DRP involves complex, interrelated mechanisms, including genetic and epigenetic factors, oxidative stress, inflammation, and the production of advanced glycation end products and VEGF.[1,3,4]

Nutrition therapy plays an essential role in the managing of DM.[5] Nutrition-based interventions show great promise as supplementary therapy for preventing or slowing down the development of diabetic retinopathy (DR) in its early stages. These interventions can be a non-invasive and cost-effective therapeutic option accessible to individuals of all socioeconomic backgrounds.[6]

The KD, characterized by a high-fat content (90%) and low levels of protein and carbohydrates, has been used as a therapeutic approach for intractable epilepsy since the 1920s.[7] These diets are believed to enhance lipid metabolism and reduce inflammatory disorders. These diets induce ketosis, which leads to the immune system adjusting to low glucose levels and a change in metabolism towards the oxidation of fatty acids in the mitochondria, resulting in ketogenesis and ketosis. This metabolic shift helps to reduce inflammation[8]. Due to the significant role of inflammation in the development of DRP, it is believed that a KD may positively affect the management and treatment of DM and, consequently, DRP.

The WD is characterized by a high consumption of saturated fats, sweets, and processed carbs. There is scientific evidence indicating that highly processed foods have detrimental effects on human health. The global excessive consumption of diets rich in saturated fats, sugars, and refined carbohydrates is a significant factor in the widespread occurrence of obesity and type 2 DM.[9]

This study aims to investigate the effects of diet on eye tissues such as retinas in streptozotocin-induced DM and fed with different diet types.

MATERIALS AND METHODS

Ethics Committee Approval: This study was prepared with the approval of the Ethics Committee of Sakarya University (Date: 07/08/2019 Decision no: 26). It complies with a Guide for the care and use of laboratory animals

Study Design: In the study, 8-10 weeks old, those with similar weight(150-200gr) 28 Long Evans male rats were randomly selected and divided into four groups. For the study, a total of four groups were formed: the control group consisting of 7 healthy, DM-free rats fed with normal rat feed (Group 1), the normal group consisting of 7 DM formed rats fed with normal rat feed (Group 2), the ketogenic group consisting of 7 DM formed rats fed with a KD (Group 3) and the western group consisting of 7 DM formed rats fed with a WD (Group 4). In order to produce DM in rats, a solution of streptozotocin (Cayman®) at a dosage of 60 mg/kg was dissolved in PBS and delivered by the intraperitoneal route[10]. Individuals with a fasting glucose level exceeding 200 mg/dl in the blood sample collected from the tail vein after 72 hours were classified as DM. Streptozotocin was re-administered in the same dose to the animals that did not meet the criteria for DM. Rats diagnosed with DM were not treated. The animals were put in group feeding and fed ad libitum. Clean water was always available in manual drinkers.

At the end of 10 weeks, after exsanguination under anesthesia, eyes were enucleated and fixed in a 10% neutral buffered formaldehyde solution. After histological tissue follow-up, 5 µm thick tissue sections were taken along the optic nerve in a randomized, double-blind manner from tissue sections embedded in paraffin blocks for histological staining methods.

Staining Methods: Before staining, the sections were incubated in an oven at 60 ^{0}C for 2 hours, deparaffinized and rehydrated in xylol for 3 times 5 minutes, in absolute alcohol for 3 minutes, in 96% alcohol for 3 minutes, in 80% alcohol for 3 minutes, in 70% alcohol for 3 minutes and in distilled water for 3 minutes.

Immunostaining and hematoxylin eosin staining methods were applied to the sections that were deparaffinized and prepared for staining with the following steps.

Immunohistochemical Staining Protocol: Deparaffinized and rehydrated sections were first subjected to antigen retrieval. For this, the pH was adjusted to 6 with HCl. Trisodium citrate (dihydrate) 2.94 g (10 mM), 1 liter distilled water, 0.5 ml tween 20 were added and mixed. The mixture was kept in an oven at 40 ^{0}C for 1 night and washed twice for 5 minutes with Tris Buffered Saline (TBS+0.025% Triton X-100) at room temperature. Blocking was performed with 10% normal goat serum diluted with TBS containing 1% BSA for 2 hours at room temperature. The area around the slides was dried without touching the tissue and scratched with pappen. Primary antibody diluted in TBS with 1% BSA was applied (+4 0C, 1 night). For caspase 3: CASP3 Polyclonal Antibody E-AB-63602 (Elabscience®), for VEGF-A: VEGF-A Polyclonal Antibody E-AB-40004 (Elabscience®) was used. TBS washing was performed 2 times for 5 minutes at room temperature. A secondary antibody diluted with 1% BSA in TBS was applied (1 hour at room temperature). It was

washed with TBS for 5 minutes. Goat anti-rabbit HRP was applied for 15 minutes at room temperature and, washed 3 times for 3 minutes with TBS and soaked in DAB substrate mixture for 7 minutes. Washed with TBS 3 times for 3 minutes at room temperature and washed in distilled water for 5 minutes. Contrast staining was performed with hematoxylin for 1 minute and, washed with distilled water and sealed with mounting medium. The extent and severity of Caspase-3 and VEGF immunohistochemical staining were visually assessed and histologically scored semiquantitatively[11]. Immunohistochemical reactions were graded as low intensity, moderately intense, and very intense based on the extent and severity of immunoreactivity in staining.

Statistical Analysis: The study used descriptive statistics for categorical and numerical variables, with the Pearson chi-square test for categorical data and One-way ANOVA for numerical data. Tukey and Tamhane T2, pairwise comparison tests, were used for significant differences. Kruskal Wallis and Dunn's tests were used for non-normal distribution data. The Shapiro-Wilk test assessed normality. The analysis was conducted using SPSS v20.0 software, with a p-value of less than 0.05.

RESULTS

The degrees of retinal staining with Caspase-3 and the number of rats in the groups are shown in Table 1. There was no significant difference between the groups (p: 0.65).

Figure 1 displays immunohistochemistry staining of the retina of diabetic rats that were given a Western diet including Caspase-3. The black arrow indicates positively stained ganglion cells (x400 magnification).

Figure 2 shows moderately intense staining with Caspase-3. Positively stained cells are indicated by the black arrow, and negatively stained cells are indicated by the white arrow (x400 magnification).

Table1. Retinal staining with Caspase-3.

		Low intense staining	Moderately intense staining	Very intense staining	p-value
Group 1 (Control) (n=7)	n	3	0	4	0.65
	%	42.9	0	57.1	
Group 2 (Normal) (n=7)	n	2	2	3	
	%	28.6	28.6	42.9	
Group 3 (Ketogenic) (n=7)	n	0	6	1	
	%	0	85.7	14.3	
Group 4 (Western) (n=7)	n	1	3	3	
	%	14.3	42.9	42.9	

n: Indicates the number of animals in the group.

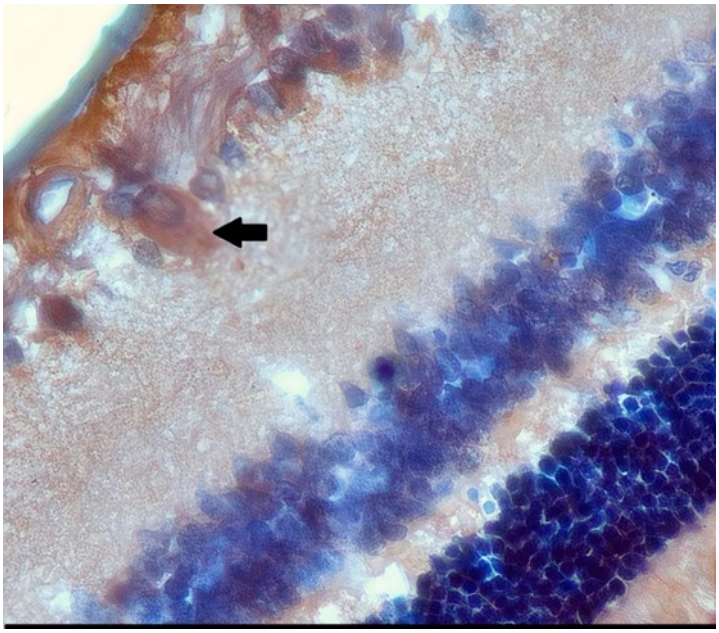

Figure 1. Immunohistochemical staining of the retina of diabetic rats fed a WD with Caspase-3. Positively stained ganglion cells are indicated by the black arrow (x400magnification).

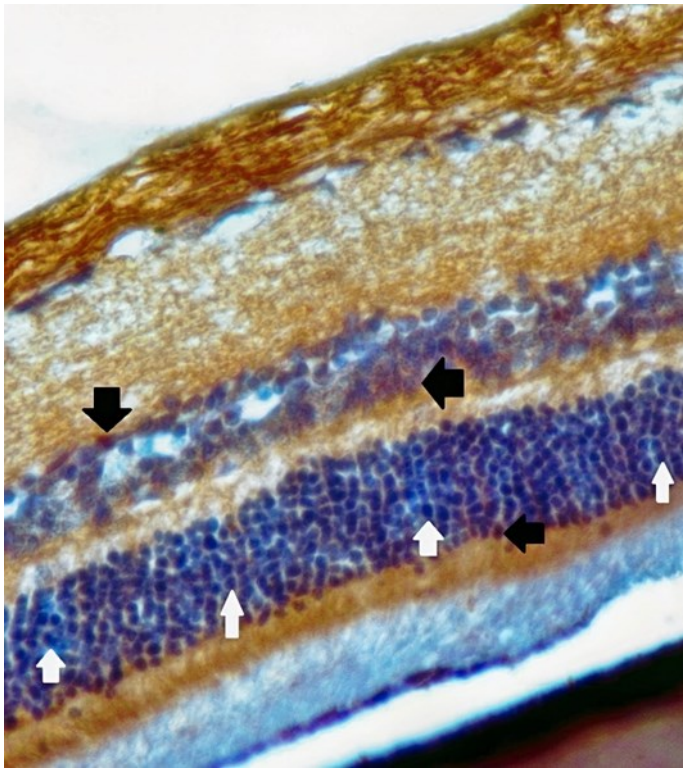

Figure 2. Moderately intense staining with Caspase-3. Positively stained cells are indicated by the black arrow, and negatively stained cells are indicated by the white arrow (x400 magnification).

The degrees of retinal staining with VEGF and the number of rats are shown in Table 2. There was a significant difference between the groups (p: 0.018). In Group 3, low-intense staining is noted at a higher rate (85.7%) than in the other groups.

The thicknesses of the retinal layers are shown in Table 3. In the comparison of the thicknesses of the retinal layers, there was a significant difference between the groups in inner nuclear, inner plexiform, ganglion and outer nuclear layer thicknesses. Significant thickening was noted in Group 4 compared to the other groups in all of these groups. The P value was <0.01 in the comparison of the inner nuclear layer, 0.006 in the comparison of the outer nuclear layer, 0.013 in the comparison of the inner plexiform layer, and 0.017 in the comparison of the ganglion layer. No statistically significant difference was seen between the groups after comparing the choroidal thicknesses (p: 0.118).

Table 2. Retinal staining with VEGF.

		Low intense staining	Moderately intense staining	Very intense staining	p-value
Group 1 (Control) (n=7)	n	2	2	3	
	%	28.6	28.6	42.9	
Group 2 (Normal) (n=7)	n	3	4	0	
	%	42.9	57.1	0	
Group 3 (Ketogenic) (n=7)	n	6	1	0	**0.018**
	%	85.7	14.3	0	
Group 4 (Western) (n=7)	n	0	4	3	
	%	0	57.1	42.9	

VEGF: Vascular endothelial growth factor; n: Indicates the number of animals in the group.

Table 3. The comparison of the thicknesses of the retinal layers.

		Group 1 (n:7)	Group 2 (n:7)	Group 3 (n:7)	Group 4 (n:7)	p-value
Choroid	Mean±SD	20.14±5.79	19.29±4.61	17.43±3.31	23.57±4.43	0.118[a]
	SV-medium-GV	12.00-19.00-29.00	12.0-21.0-24.0	14.0-16.0-23.0	17.0-24.0-29.0	
Outer nuclear	Mean ±SD	25.57±7.63	20.43±4.61	19.86±4.18	29.71±2.06	**0.006**[b]
	SV-medium-GV	19.00-23.00-40.00	14.0-22.0-27.0	13.0-22.0-23.0	26.0-30.0-33.0	4>3 (0.013) 4>2 (0.018)
Inner nuclear	Mean ±SD	13.29±4.31	12.29±4.79	9.86±2.34	21.71±5.74	**<0.001**[a]
	SV-medium-GV	7.00-14.00-20.00	7.0-13.0-19.0	7.0-9.0-14.0	13.0-23.0-27.0	4>1 (0.009) 4>3 (>0.001) 4>2 (0.003)
Inner plexi-form	Mean ±SD	18.14±11.05	17.57±7.81	14.71±5.38	40.57±15.15	**0,013**[b]
	SV-medium-GV	7.00-15.00-37.00	9.0-16.0-29.0	9.0-13.0-23.0	17.0-44.0-53.0	4>3 (0.018)
Gangli-on	Mean ±SD	9.86±4.02	8.29±1.98	8.00±2.71	14.43±3.15	**0.017**[b]
	SV-medium-GV	6.00-8.00-17.00	6.0-9.0-11.0	5.0-7.0-13.0	8.0-15.0-17.0	4>3 (0.019)

n: Indicates the number of animals in the group; SD: Standard deviation; SV: Smallest value; GV: Greatest value; a: One-way ANOVA; [b]: Kruskal Wallis Test.

DISCUSSION AND CONCLUSION

The KD has been shown to improve glycemic control, reduce weight, and enhance lipid profiles in patients with type 2 DM, which may indirectly benefit DRP by improving overall metabolic health.[12-14] The KD is effective in managing DM by regulating glucose and insulin levels, which could potentially help in controlling DRP by stabilizing blood sugar levels.[12,15,16] In diabetic mice, the KD reduced pain, improved sensory thresholds, and normalized epidermal innervation, suggesting potential benefits for diabetic neuropathy, which shares some pathophysiological mechanisms with DRP.[17]

To the best of our knowledge, our study is the first study on the effects of KD and WD on DRP in rats. For this reason, there is no study that we can compare directly. However, the study published by A.Al -Khalifa et al. in 2010, in which they investigated the effects of KD in rats, stated that there was no difference in diabetes in the KD group compared to the control group, and they concluded that the KD-protected from diabetes.[18] Similarly, the control group and KD group showed similar findings in our study. In addition to this, in our study, negative effects of WD were observed. In the study published by Barakat A. et al. in 2019, a plant-based, high-fat, low-sugar diet, in contrast to the WD, does not exacerbate retinal endothelial damage in streptozotocin-induced diabetes.[19]

Increased inflammatory mediators in those with DRP may be tissue edema, particularly as a result of increased vascular permeability due to VEGF. When the retinal thicknesses were compared in our study, it was observed that the inner nuclear layer, inner plexiform layer and ganglion layer thicknesses were significantly thicker in Group 4 than in the other groups. Based on this finding, we can say that WD worsens DRP. In addition, in retinal tissue staining, staining with VEGF was more intense in Group 4. This also supports the increase in thickness mentioned above.

When the choroidal thicknesses were compared, no significant difference was observed between the groups. Although there is no animal study that we can compare directly in this way, some clinical studies yielded different results from our study. Some studies suggest choroidal thickness increases in the early stages of DRP and with advanced retinopathy, while other studies suggest it decreases with progression and in cases of diabetic macular edema or proliferative diabetic retinopathy (PDRP).[20,21]

It is known that there may be regional differences in choroidal thickness. In this case, it can be concluded that there is no choroidal involvement. However, since histological sections were evaluated in our study, the anatomical region through which the section passed may not have been standardized between the groups.

The absence of a significant difference in choroidal thicknesses in our study may be coincidental. Moreover, reasons such as the inability to standardize the tissue through which the sections pass, the comparison of living tissue and dead tissue, the differences between the human eye and the eye of the experimental animal, and the choroidal structure may also have contributed to this.

There are some limitations of this study; we could not use additional methods to confirm VEGF and Caspase-3 staining due to limitations in our capabilities. Our photo quality may be a bit low due to our low capacity to photograph histological sections. We did not count cells during histo-scoring, so our scoring results may not be quantitative.

In conclusion, since the rate of low-intensity dye

uptake was found to be high in Group 3 and the rate of intense staining was found to be high in Group 4 in retinal staining with VEGF, it can be concluded that the KD affects the intraocular structures less than the destructive effect of diabetes compared to the WD. All these situations are valid within the current period of our study, and how they will result in the long term should be evaluated in longer-term experimental and clinical studies.

Ethics Committee Approval: Our study was approved by Sakarya University (Date: 07/08/2019 Number: 26). Complies with Guide for the care and use of laboratory animals. The study was carried out following the international declaration, guidelines.

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – HIS, IY, NC; Supervision – IY, EÇ, NC; Materials – HIS, NC; Data Collection and/or Processing –HIS, NC; Analysis and/or Interpretation – GO; Writing –HIS, IY, NC, BGS.

Peer-review: Externally peer-reviewed.

Other Information: This study was presented as an oral presentation at the 56th Turkish Ophthalmology Association National Congress on 2nd-6th of November 2022, Antalya.

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