DOI:10.14744/bej.2024.67199
Beyoglu Eye J 2024; 9(4): 228-234

Original Article

Comparison of Choroidal Vascularity Index, Retinal, and Optic Nerve Changes in Diabetes Mellitus Patients Without Diabetic Retinopathy

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Abstract

Objectives: To report changes in the choroid, optic nerve, and macula in diabetes mellitus patients without diabetic retinopathy, and to compare these findings with age and sex-matched healthy volunteers. Furthermore, the duration of the disease was recorded and the impact on these parameters was aimed to be analyzed.

Methods: In this study, 60 right eyes of diabetes mellitus (DM) patients without diabetic retinopathy who applied to our department for routine examination were enrolled. To evaluate the peripapillary retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL), Swept-Source Optical Coherence Tomography imaging was performed. In addition, images were recorded and processed by the image-j program and the 'choroidal vascularity index' (CVI) was calculated. The measurements were compared with 60 right eyes of age-sex-matched healthy volunteers. Furthermore, the patient group was divided into 2 subgroups according to disease duration and the measurements were compared with each other as well.

Results: Both RNFL and GCL thickness values were observed to be thinner in DM patients group compared to the control group. CVI was found to be lower in DM group compared to the control group. In addition, the duration of the disease was significantly associated with the RNFL and GCL thinning and lower CVI.

Conclusion: DM can lead to a decrease in RNLF and GCL thickness and also a decrease in CVI which can impair visual acuity even in the absence of diabetic retinopathy. Therefore, monitoring changes in the optic nerve, retina, and choroid layer is crucial in these patients.

Keywords: Choroidal vascularity index, diabetes mellitus, optic nerve

Introduction

Diabetes mellitus (DM) is a global growing disease that affects more than 400 million people worldwide and this number is estimated to increase up to 642 million by the year 2040 (1). It is well known that diabetic retinopathy (DR) is one of the most common and dangerous microvascular complications of DM and is considered one of the leading causes of blindness among productive-aged adults in the industrialized and developed world (2). Due to this fact, it is crucial to provide early diagnosis and prompt treatment whenever necessary.

To provide early diagnosis and treatment, recent studies like this current study, focus on retinal changes in diabetic patients without classic retinopathy signs and emphasize the

How to cite this article: Kiyat P, Karti O. Comparison of Choroidal Vascularity Index, Retinal, and Optic Nerve Changes in Diabetes Mellitus Patients Without Diabetic Retinopathy. Beyoglu Eye J 2024; 9(4): 228-234.

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Submitted Date: April 22, 2024 **Revised Date:** September 14, 2024 **Accepted Date:** October 23, 2024 **Available Online Date:** December 11, 2024

Beyoglu Eye Training and Research Hospital - Available online at www.beyoglueye.com

importance of understanding the pathogenesis to find out efficient diagnosis and treatment strategies (3). As examples, both Lim et al.'s (4) study and Simo et al.'s (5) study suggested that in DM patients without DR, significant neurodegeneration-related changes were detected and these changes were suggested to contribute microvascular damage.

Swept-Source Optical Coherence Tomography (SS-OCT) is a widely accepted, rapid and non-invasive device that uses the low coherence interferometry technique (6) to produce cross-sectional images of the retina and optic nerve head. With the SS-OCT device, it is possible to obtain high-definition retinal and choroidal images with the speed of 100,000 A-scans and 8-µm axial resolution (7). The coherent laser light and the reflection from various ocular structures with different optical properties allow us to analyze layers in detail. SS-OCT imaging gives information about retinal layers' thicknesses and it can detect specific changes, such as axonal loss or ganglion cell loss by measuring the retinal nerve fiber layer (RNFL) thickness and ganglion cell layer (GCL) thickness (8). Furthermore, it is possible to measure the thickness of the choroid with SS-OCT in an objective and reliable manner which helps to determine and classify the changes in the choroidal vessels in several diseases (9).

The choroidal vascularity index is another entity that can be calculated by a specific analysis that uses choroidal images obtained by SS-OCT. It is defined as the ratio of the choroidal luminal area to the total choroidal area (10). This technique helps to measure choroidal vascularity quantitatively and overcomes the several limitations of using choroidal thickness alone (11). Furthermore, in recent studies, CVI was considered a more reliable and consistent measurement technique in evaluating the choroidal structures when compared to measuring choroidal thickness alone (10,12).

This current study aims to report the choroidal changes by evaluating CVI, changes in the optic nerve by evaluating peripapillary RNFL, and changes in the macula by evaluating GCL in DM patients without DR, and to compare these findings with age and sex-matched healthy volunteers. Furthermore, the duration of DM was recorded and the impact on these parameters was aimed to be analyzed.

Methods

This study was approved by the institutional review board of the Buca Seyfi Demirsoy Training and Research Hospital (Date: 23.08.2023; Number: 2023/8-155) and adheres to the tenets of the Declaration of Helsinki. Each subject provided written informed consent. After institutional review board approval, 60 DM patients who applied to İzmir Democracy University Buca Seyfi Demirsoy Training and Research Hospital Department of Ophthalmology for routine examination were enrolled in this study.

Patients with any sign of DR detected with clinical examination or SS-OCT imaging, and patients who were already treated with DR diagnosis were excluded. Patients who had any other systemic diseases that can affect the retina or choroid, or patients with conditions that can cause alterations in the ocular circulation, such as smoking, pregnancy, or breastfeeding, were excluded. Patients using any kind of topical or systemic drug except insulin or oral anti-diabetics were excluded as well. Patients with any pathology that could cause measurement failures such as severe cataract, glaucoma, congenital or acquired retinal abnormalities, refraction errors higher than ±3 D, nystagmus, corneal opacity, and patients with ocular surgery or trauma history were also excluded.

All patients were performed a detailed ophthalmological examination including best corrected visual acuity determination with the Snellen chart, intraocular pressure measurement with applanation tonometry, and anterior-posterior segment evaluation with slit-lamp biomicroscopy. After the examination, SS-OCT (DRI-OCT Triton, Topcon, Inc, Tokyo, Japan) images were taken to evaluate RNFL thickness values in 4 quadrants and GCL thickness values in 6 quadrants. Choroidal images were used to calculate CVI. The measurements were evaluated blindly by the same ophthalmologist.

To evaluate the RNFL and GCL thickness values in each group, the SS-OCT device's automatic calculation and reporting system was used, and the thickness values of 4 quadrants (superior, temporal, inferior, and nasal) for RNFL, and 6 quadrants (superior, superotemporal, superonasal, inferior, inferotemporal, and inferonasal) for GCL were recorded (Fig. 1).

For analyzing the CVI, the SS-OCT images through the fovea were selected for image binarization and segmented using the protocol described by Agrawal et al. (13) by using the image processing program-Image J version 1.53 a (National Institutes of Health, Bethesda, MD, USA). The polygon selection tool helped to detect the total choroidal area (TCA) between the retinal pigment epithelium and choroid-scleral junction for the subfoveal region within a width of 1500 µm (750 µm either side of the fovea). Regions of interest (ROIs) were added to the ROI manager. After converting the image into 8 bits, a Niblack autolocal threshold tool was applied. This tool helped to get the mean pixel value with the standard deviation (SD) for all the points. The luminal area (LA) was defined by using the color threshold tool and was also added to the ROI manager. To determine the area of vascularity within the selected polygon, both areas in the ROI manager were selected and merged through an "AND" operation. CVI value was defined as the ratio of LA to TCA. To avoid the diurnal alterations in the choroidal measurements, all scans were performed at the same time of day, between 10:00 and 12:00 a.m., for each patient and the volunteer group (Fig. 2).

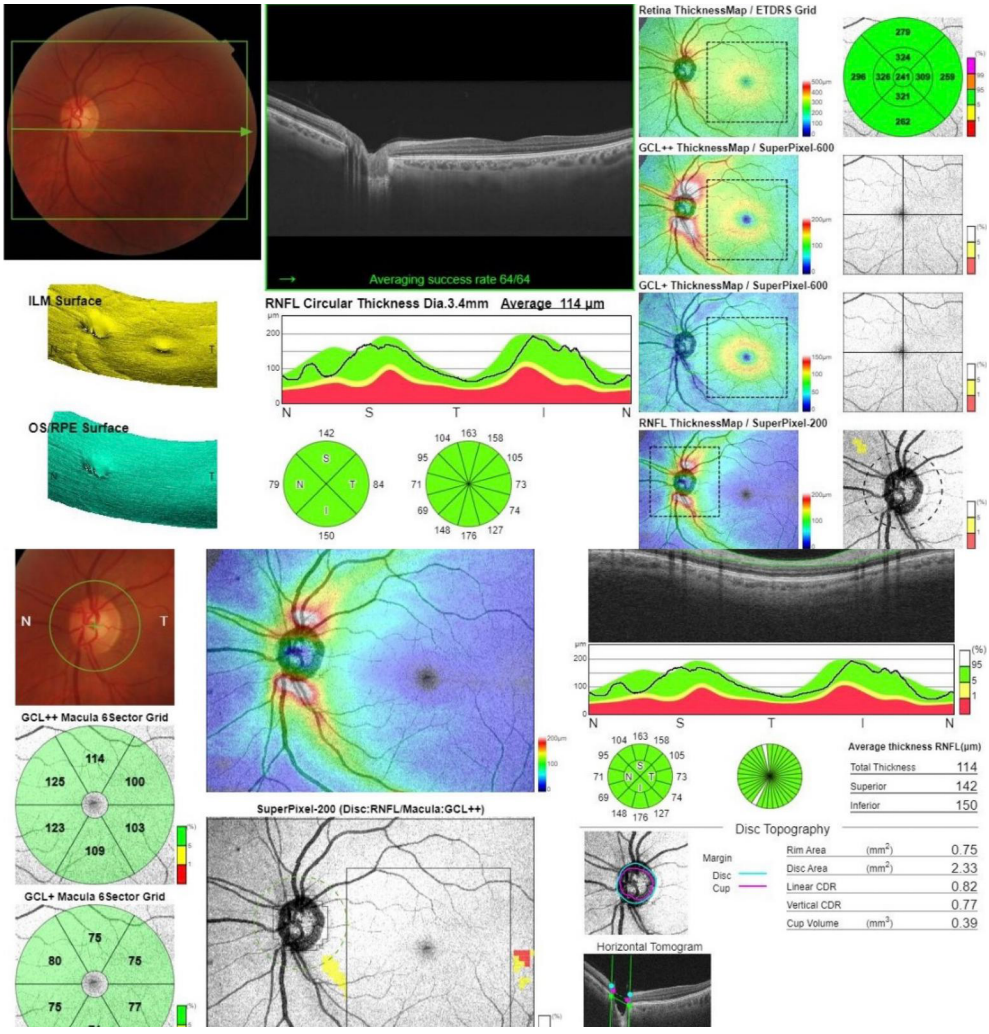

Figure 1. Print of SS-OCT device's automatic calculation and reporting system showing RNFL and GCL values.

The DM without DR group was divided into 2 subgroups according to the previous studies (14-17). Group 1 was defined as the patients with disease duration of more than 5 years. Group 2 was defined as the patients with disease duration of 5 years or shorter. The measurements of group 1 and group 2 patients were compared with each other as well as the measurements of 30 age-matched healthy volunteers who visited the İzmir Democracy University Buca Seyfi Demirsoy Training and Research Hospital Department of Ophthalmology for routine examinations and this last group was defined as group 3.

Statistical Analysis

'IBM The Statistical Package for the Social Sciences version 25' (SPSS Inc., Chicago, IL, USA) was used for statistical purposes. Categorical variables were expressed as frequency and percentage, and numeric variables as mean and standard deviation. Kolmogorov–Smirnov tests were used to determine whether the data were normally distributed. Analysis of variance (ANOVA) testing was performed to evaluate differences in normally distributed data. Kruskal–Wallis test and Mann–Whitney U test were performed to determine differences in non-normal distribution. A P-value under 0.05 was considered statistically significant. For statistical purposes, values from the right eye were analyzed in both the study and control groups.

Results

In our study, there were 30 (14 male, 16 female) patients in group 1, 30 (14 male, 16 female) in group 2, and 30 (13 male, 17 female) in group 3. The mean age was 59.9±7.6 in group 1, 59.8±8.2 in group 2, and 59.4±9.8 in group 3. There was no statistically significant difference between the groups in terms of gender and age (p=0.956, p=0.982, respectively).

The RNFL, GCL, and CVI values of group 1, group 2, and group 3 were summarized in Table 1. In RNFL comparisons, while the RNFL thickness was thinner in all quadrants in group 1 when compared to the control group, statisti-

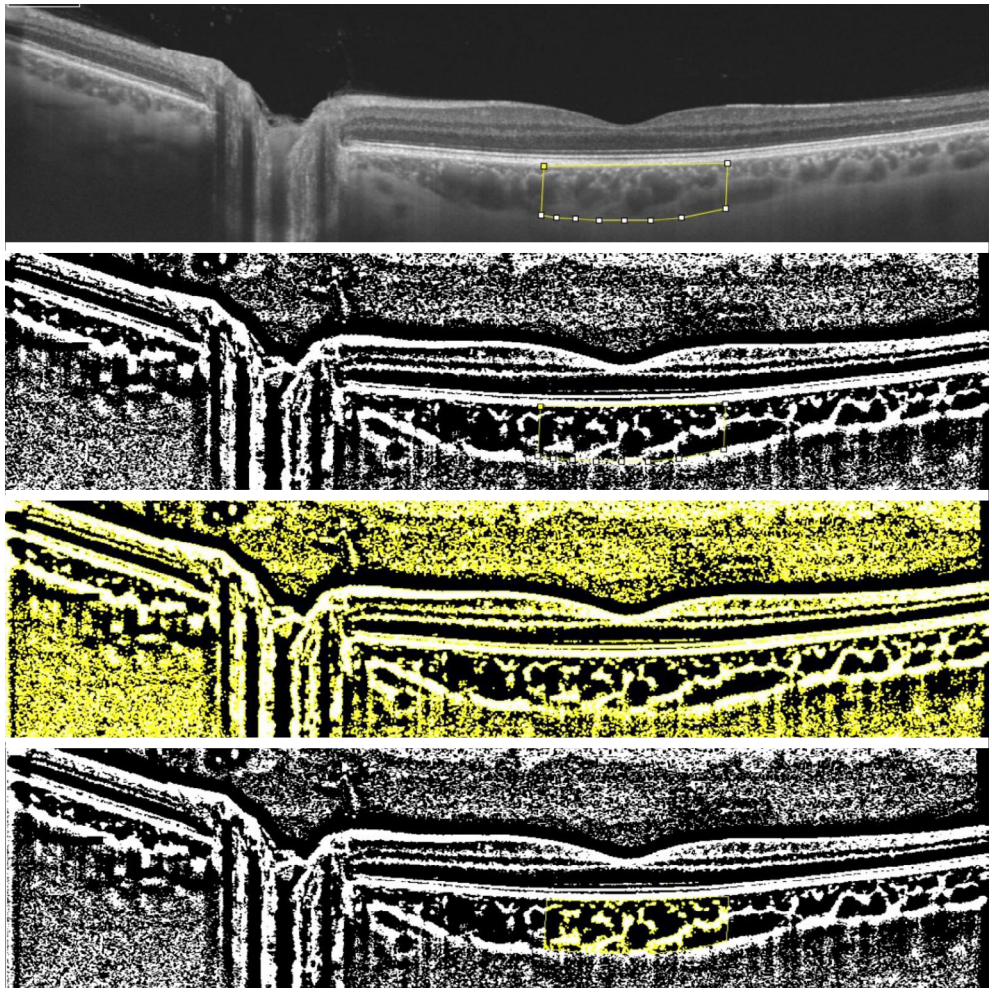

Figure 2. Choroidal vascularity index calculation using Image-J program.

cal significance was only observed in the superior quadrant (p=0.045). In addition, RNFL thickness values were detected thinner in all quadrants in group 2 when compared to the control group however, no statistically significant difference was found.

GCL thickness was observed to be thinner in all quadrants of both group 1 and group 2 when compared to group 3. A statistically significant difference was detected in an inferior quadrant in comparison of group 1 and group 3 (p<0.0001). In addition, statistically significant differences were detected in superior, superotemporal, superonasal, and inferior quadrants in comparison of group 2 and group 3 (p<0.0001, p=0.001, p=0.024, p=0.010, respectively) Furthermore, CVI was also detected statistically significantly lower in group 1 and group 2 when compared to group 3. (p=0.017, p<0.0001)

When group 1 and group 2 were compared, there were statistically significant differences in superior, superotemporal, and inferior quadrant GCL thickness and CVI, these values were detected lower in group 1 (p=0.003, p=0.005, p<0.0001, p=0.002, respectively).

Discussion

In this current study, DM patients without DR were found to have a statistically significantly lower CVI when compared to the healthy subjects. In literature, Aksoy et al.'s, (18) Kim et al.'s (11), and Tan et al.'s study (12) also reported similar results in terms of reduced CVI values in the same patient group.

Choroidal changes might be related with choroidal hypoxia and choriocapillary loss. Ischemic changes in choroidal vasculature and vasoconstriction might be the main responsible reasons for the decrease in CVI values (11). In an animal model, an impairment in choroidal blood flow was mentioned as an early pathologic change in DM (19). It was also reported that a decrease in choroidal blood flow occurred in DM patients before the development of retinopathy (20). Choroidal evaluation in DM patients has an important role in preventing further complications including DR. However it is important to emphasize the difference of imaging techniques. In literature, most studies used the 'Enhanced Depth of Imaging' (EDI)-OCT technique which is a feature of the Spectral-Domain (SD) OCT. However, the blur in the choroid-scleral

Table 1. Comparison of RNFL, GCL, and CVI Values of Groups

	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Control Group (Mean±SD)	P[a]	P[b]	P[c]	P[d]
RNFL (μm)							
Superior	122.7±16.0	131.1±15.0	133.6±21.6	0.220	0.045	1.000	0.042
Inferior	136.7±12.2	135.5±12.5	142.8±16.7	1.000	0.185	0.850	0.061
Nasal	81.2±15.1	81.6±17.3	88.9±14.1	1.000	0.093	0.116	0.052
Temporal	72.8±13.7	78.8±11.2	80.0±13.9	0.251	0.117	1.000	0.086
GCL (μm)							
Superior	103.2±7.8	108.1±7.2	111.4±12.2	0.003	0.162	0.000	0.001
Superotemporal	87.7±14.1	94.8±6.8	97.3±11.5	0.005	0.245	0.001	0.001
Superonasal	115.9±10.2	119.2±6.7	121.7±10.6	0.137	0.311	0.024	0.062
Inferior	102.8±11.6	106.9±8.2	109.0±13.8	0.000	0.000	0.010	0.000
Inferotemporal	90.3±23.5	94.4±13.8	99.0±14.4	0.947	0.118	0.122	0.198
Inferonasal	116.8±9.9	117.8±6.8	121.1±10.8	1.000	0.190	0.426	0.146
CVI	61.3±4.2	64.8±4.7	67.4±4.1	0.002	0.017	0.000	0.000

RNFL: Retinal nerve fiber layer; GCL: Ganglion cell layer; SD: Standard deviation; CVI: Choroidal vascular index. a: Group 1-Group 2, b: Group 1- Group 3, c: Group 2- Group 3, d: Group 1-Group 2- Group 3.

interface potentially results with measurement bias. On the other hand SS-OCT, with its higher resolution and speed than EDI SD-OCT, and with the technology reducing the retinal pigment epithelium-related dispersion by using a longer laser wavelength, prevents the blur in the choroidal-scleral interface and provides higher-quality images and helps to get a reliable measurement (21). Furthermore, it is important to emphasize, the choroidal measurements are not interchangeable between the SS-OCT and SD-OCT. In literature, a study by Pinilla et al. (21) reported that choroidal thickness values were detected higher with SD-OCT than those with SS-OCT. Although different values were obtained from the two devices, the correlation between their measurements was reported as high. In another study by Matsuo et al. (22) reported controversial results such as higher values detection with SS-OCT compared to SD-OCT. In another study by Philip et al. (23) reported higher values with the SD-OCT when compared to SS-OCT. They also found strong agreement between the two devices. Finally, in Copete et al.'s study, (24) lower values were detected with the SS-OCT when compared to SD-OCT. This fact should be taken into consideration when different devices are used to evaluate the choroid.

However, analyzing choroidal thickness as a marker might cause some discrepancies and has low reproducibility and reliability due to the alterations in choroidal thickness related to various factors including age, gender, systolic blood pressure, or diurnal variations (25). For those reasons, CVI may be a more stable and appropriate marker in evaluating choroidal vascularity.

It is well known that diabetes-related microvascular complications are associated with disease duration. In previous studies, it was simply proved that the disease duration is an important factor in the development of complications (26). In our study, DM patients without DR who had a disease duration of more than 5 years were found to have lower CVI values when compared to the patients with less duration. Similar to this current study, in another study, (27) DM patients with a disease duration of more than 5 years were detected to have lower CVI in Sattler's layer when compared with those with a disease duration of less than 5 years. Furthermore, Endo et al. (28) reported similar results and reported that patients with longer disease duration of DM showed more reduction of CVI compared to those with shorter duration.

Neurodegeneration has been considered one of the main mechanisms in the pathogenesis of DM and previous studies showed alterations in RNFL thickness in DM patients (29). Current study's results in terms of RNFL changes were in accordance with the majority of the previous studies. In our study, RNFL thickness was detected to be thinner in DM patients without DR when compared to healthy individuals. Similar to this current study, in Dhasmana et al.'s study, (30) it was reported that RNFL thickness was found to be thinner in DM patients especially in the superonasal and superotemporal quadrant when compared with healthy individuals, while an-

other study by Garcia-Martin et al. (31) also reported significant thinning in RNFL especially in inferior and inferotemporal quadrants. Mehboob et al. (32) reported a significant decrease in RNFL in all quadrants in patients with DM without DR compared to controls. In a study by Lee et al., (33) patients with DM were shown to have significantly thinner GCL. And in Pekel et al.'s study, (34) it was revealed that DM patients without DR were detected to have thinner GCL when compared to healthy controls. In summary, previous studies and this current study found that even in the absence of microvascular diabetic changes, GCL and RNFL thickness values were detected significantly thinner in eyes with DM.

In DM, many metabolic abnormalities occur in the retina, such as increased levels of glutamate (35) and increased oxidative stress (36). These changes were reported to cause apoptosis in neuronal cells in patients with DM. In addition, experimental studies reported that the retina of DM patients without DR was detected to have immunoreactivity to apoptosis-related factors in ganglion cells (37). A rising assumption occurred that DM might induce apoptosis of retinal neural cells and activation of glial cells, which gave rise to GCL and RNFL thinning. When the duration of the disease was analyzed, the current study's analyses were in line with previous studies which showed that the disease duration of DM had an inverse relation with RNFL thickness, which means the RNFL was found to be thinner with the disease duration (38,39). In Lee et al.'s study, (3) DM patients without DR were detected to have thinner RNFL and damages were more severe in patients with disease duration more than 10 years.

Limitations of this study include the small number of patients and the control group, lack of data related to HbA1c, blood glucose levels, or the information about the long-term follow-up of the DM.

On the other hand, we believe that the results of this current study can be evaluated as a benchmark to detect early alterations in the optic disc, macula, and choroid before the development of DR. In literature, previous studies may have analyzed only one of these features however, our study is the only one, up to date that evaluated and analyzed choroidal, macular, and optic disc parameters altogether.

Conclusion

The current study showed that GCL and RNFL thickness in patients with DM without DR were found to be decreased, and the duration of the disease was significantly associated with the thinning. The clinical relevance of this result is neurodegeneration in DM is a significant phenomena and can play a crucial role in preventing the development of DM complications. In addition to these findings, CVI was also found significantly lower in DM patients without DR when compared to healthy individuals and the longer disease duration group was detected to have lower CVI which emphasizes the importance of disease duration in both vascular dysregulation and neurodegeneration-related complication development. It is crucial to remember that early detection and prevention of diabetic ocular complications is the most important factor in maintaining vision. Monitoring the alterations of retinal layers and CVI may help detecting initial damage of DM and can be considered as valuable markers.

Disclosures

Ethics Committee Approval: İzmir Buca Seyfi Demirsoy Training and Research Hospital Ethics Committee (Approval date and number: 23.08.2023 2023/8-155).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Use of AI for Writing Assistance: Not declared.

Authorship Contributions: Concept – P.K.; Design – P.K., O.K.; Supervision – O.K.; Materials – P.K.; Data collection and/or processing – P.K., O.K.; Analysis and/or interpretation – P.K., O.K.; Literature search – P.K.; Writing – P.K.; Critical review – O.K.

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