RESEARCH ARTICLE

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Optical Coherence Tomography Findings in Cannabis Users

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SUMMARY

Objective: In this study, we aimed to evaluate the effects of cannabis use on the retinal nerve fiber layer (RNFL) and the macular ganglion cell – inner plexiform layer GCL-IPL using optical coherence tomography (OCT).

Method: This prospective, comparative study included 26 cannabis users who were evaluated at the Psychiatry Outpatient Unit of Muş State Hospital and 27 age and gender matched healthy controls. OCT was performed on both groups. The RNFL and GCL - IPL thicknesses, measured automatically by OCT, were recorded and compared between the groups.

Results: The sociodemographic parameters of the two groups did not differ. The mean retinal nerve fiber thickness and thickness at the superior, nasal, inferior quadrants were not significantly different; but there was a significant difference at the temporal quadrant (p=0,022). In the analysis of macular ganglion cell – inner plexiform layer, the mean values as well as the infetotemporal, inferior, inferonasal and superonasal quadrants did not show significant differences. But there was a statistically significant decrease in the superior and superotemporal quadrants (p=0,006, p=0,027).

Conclusion: These findings suggest that cannabis use leads to the thinning on retinal layers. As it is an easily observable part of the brain, evaluating retinal nerve fiber and ganglion cell layer with OCT may be important for monitoring toxic and degenerative effects in cannabis users.

Keywords: Optical coherence, cannabis, retinal nerve fiber

INTRODUCTION

Cannabis is the most commonly consumed illegal drug with over 180 million users worldwide (Lorenzetti et al. 2019). There has been an increasing trend in cannabis use with the developments in the legalisation process and social acceptance (Lowe et al. 2019). Hence, investigation of the effects of cannabis use has found a prominent place among the current topics of research. Many studies have reported the correlation of cannabis use with psychopathological disorders such as depression, anxiety, psychosis and cognitive dysfunctions (Adamson and Sellman 2003, Chye et al. 2017, Lorenzetti et al. 2019a). Also, cannabis use has been known to cause morphological and functional changes in the brain. Cannabis exerts its effects on the central nervous system through its primary psychoactive component Δ9-tetrahidrokannabinol (THC) and particularly via the CB1 receptors (Downer et al. 2001). The down regulation of CB1 receptors in chronic cannabis use has been suggested to underly the observed cognitive impairments (Fridberg et al. 2010, Sewell et al. 2010). Lorenzotti et al. (2019a) showed that cannabis use leads to a decrease in grey matter volume in the brain regions with high concentrations of CB1 receptors, such as the hippocampus, prefrontal cortex, amygdala, and the cerebellum. In the current practice, it has been possible to obtain retinal images in the form of optical biopsy by using the non-invasive and fast method of optical coherence tomography that enables the measurement of the thickness and detailed evaluation of the retinal layers. The retina is accepted a the continuation of the central nervous system with its multiple neuronal layers synapting with one another and sharing the same embryonic origins (Khalil et al. 2017, Méndez-Gómez et al. 2018). Thus, OCT imaging of the RNFL comprising the axons of ganglion cells and GCL-IPL consisting of the dendrites has recently become an important parameter in the evaluation of neurodegeneration (Kalenderoğlu et al. 2016, Mehraban et al. 2016).

Many studies have reported decreased retinal nerve fiber thickness in neurodegenerative conditions, such as Alzheimer's disease, Parkinson's disease, and Schizophrenia (Garcia-Martin et al. 2014, Lee et al. 2013, Mutlu et al. 2018). In the light of these data, it has been aimed to evaluate, by

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means of optical coherence tomography, the structural effects on RNFL and GCL-IPL of cannabis which was previously shown to have morphological and functional effects on the central nervous system.

METHOD

Cannabis User and Control Group

The study included 26 individuals under probation for cannabis use, who consulted consecutively the Psychiatry Department of Muş State Hospital between January 2016 and April 2016; and age and gender matched 27 healthy individuals, not on cannabis and consulting consecutively the department of opthalmology for medical reports (required for employment, driving license, etc.) as the control group. Written consent for participation of both groups of individuals, given detailed information about the study, were obtained before inclusion in the study. All participants were evaluated clinically on the basis of the DSM-5 diagnostic criteria for psychiatric disorders by a mental health and diseases specialist.

Demographic data of all participants, including age, gender, and duration of cannabis use were recorded. The exclusion criteria of the study were alcohol and drug use disorder in addition to cannabis use, psychiatric comorbidity, neurological or systemic disorders, previous history of head trauma and/or ophthalmological pathologies such as glaucoma, retinal diseases and refractory disorders in both groups determined after detailed ophthalmological examination including autorefractometry, tomometry, best corrected visual acuity, biomicroscopy and fundoscopy. The left eyes of the participants were used for statistical analysis.

Optical Coherence Tomography

Ganglion cell complex (GCC) and RNFL measurements were performed by a trained and experienced opthalmologist using a spectral domain OCT (Cirrus HD OCT, Carl Zeiss Meditec, Dublin, CA, USA). All eyes were dilated with tropicamide 1% before recording. Images with signal strength of 6 or higher were used analysis. RNFL measurements were achieved by centering the 3.4 mm screening circle over the optic disc (optic disc cube 200 × 200 protocol). The mean RNFL thicknessand the mean RFNL thicknesses of the superior, inferior, temporal, and nasal quadrants calculated by the device software were analyzed (Figure 1). The Cirrus HD OCT ganglion cell analysis protocol (Macular Cube 512 x 128 protocol) was used for GCC measurements. The GCL-IPL was separated automatically by the device from the other retinal layers under the name of GCC and the mean GCC thickness was reported together with the GCC thickness values in the superior, superotemporal, inferotemporal, inferior, inferonasal and inferotemporal quadrants (Figure 2).

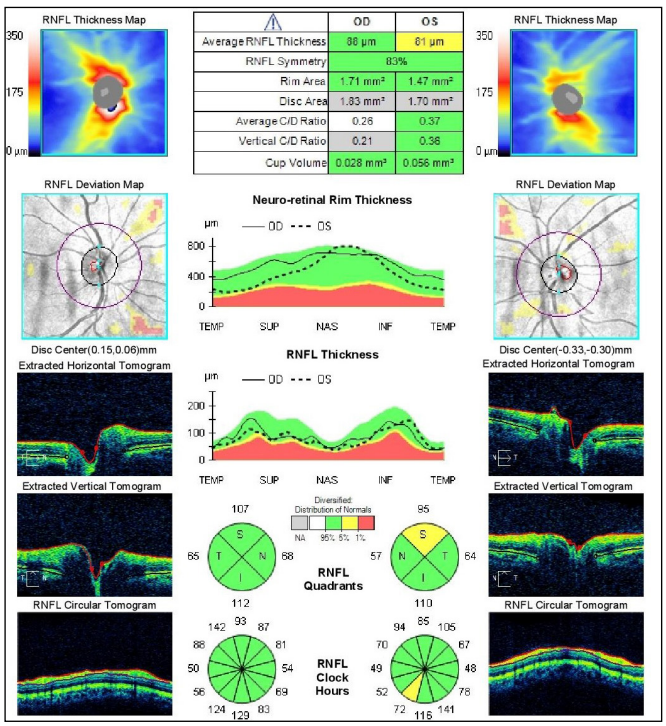

Figure 1. RNFL analysis by OCT in the eye of a cannabis using participant.

The mean RNFL thicknesses for the right (OD) and the left (OS) eyes are shown at the top; the RNFL quadrants and sectors are shown for both eyes in the middle and at the bottom. The numbers show RNFL thicknesses of the respective regions.

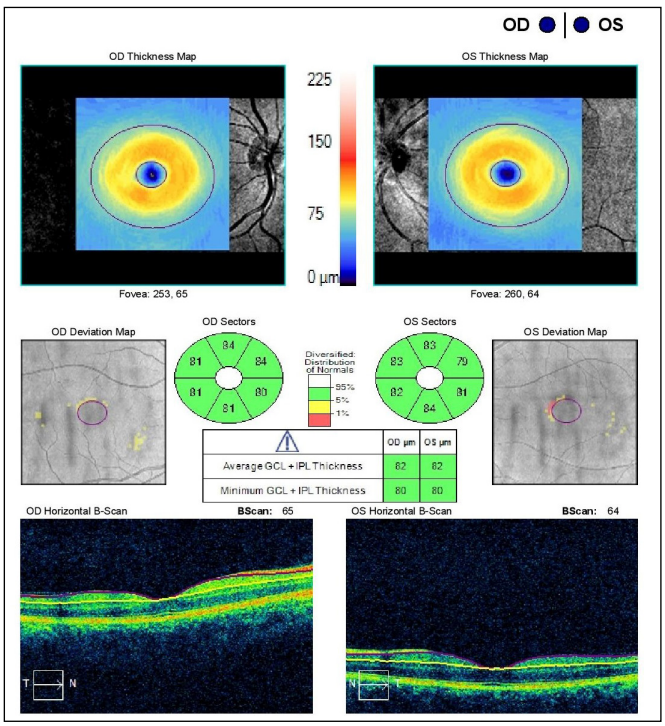

Figure 2. GCL-IPL analysis by OCT in the eye of a cannabis user participant.

The GCL-IPL sectors for the right (OD) and left (OS) eyes and the thicknesses for these regions are schematically shown in the middle. The mean thicknesses for both eyes are shown below.

Table 1. Retinal Nerve Fiber Thicknesses of the Cannbis User and the Control Groups

	Cannabis User Group		Control Group		p
Quadrants	**Mean±SD**	**Med.(Min-Max)**	**Mean±SD**	**Med.(Min-Max)**	
RNFL, Mean	97.5±9.2	98(82-115)	99.2±8.9	99(81-114)	0.501
Superior	124.2±13.1	126(94-142)	126.2±13.0	127(95-148)	0.574
Temporal	62.7±9.3	61(48-79)	68.0±7.1	69(53-80)	0.022*
Inferior	131.5±17.2	131(105-169)	128.9±14.3	128(105-162)	0.562
Nasal	72.0±11.9	70(58-116)	73.6±12.5	73(54-100)	0.618

*: Statistically significant, p< 0.05

Table 2. Macular Ganglion Cell-Internal Plexiform Layer Evaluation of the Cannabis User and Control Groups

	Cannabis User Group		Control Group		p
Quadrants	**Mean±SD**	**Med.(Min.-Max.)**	**Mean±SD**	**Med.(Min.-Max.)**	
MGC-IPL, Mean	86.6±5.4	87(77-97)	89.3±4.3	88(82-99)	0.054
Superior	86.6±5.5	86(77-98)	90.8±5.1	91(81-103)	0.006*
Superotemporal	84.6±5.7	83(75-94)	68.0±7.1	69(53-80)	0.027*
Inferotemporal	87.1±6.0	87(77-98)	89.2±4.5	88(81-97)	0.150
Inferior	86.3±6.1	87(76-98)	88.0±4.7	87(80-97)	0.259
Inferonasal	87.0±5.8	86(75-97)	89.1±5.0	89(81-100)	0.182
Superonasal	87.6±5.4	88(77-100)	90.3±4.9	90(83-102)	0.067

*: Statistically significant, p< 0.05

Statistical Analysis

Data analyses were made on the SPSS 24.0 software. The mean, standard deviation, median, minimum, maximum, frequency and ratio values were used for the descriptive statistics of the data. The Kolmogorov-Smirnov test was used to test the conformance of quantitative variables with normal distribution statistics. The independent group t-test was used to analyse the variables with normal distribution. The Mann-Whitney U test was used for the inter-group comparisons of the mean values of the variables without normal distribution. The Pearson's correlation analysis was used for variables with normal distribution and the Spearman correlation analysis was used for variables without normal distribution to assess the correlation between the duration of cannabis use and the quantitative data of the users. The results were evaluated within a confidence interval of 95% and a p value of <0.05 was accepted as statistical significance.

Ethics

The ethical approval No. 24 / 01.04.2016 was given by the Ethics Committee of Bakırköy Dr. Sadi Konuk Research and Training Hospital; and the study was conducted in accordance with the World Medical Association Helsinki Declaration.

RESULTS

All participants of the study were male. A total of 53 eyes of the 26 cannabis users and 27 controls were included in the analyses. The mean age of the cannabis user and the control groups were, respectively 23.6±3.9 years and 24.2±4.3 years, and did not differ significantly (p=0.665).

The mean RNFL thickness evaluated in the superior, temporal, inferior and nasal quadrants showed significant thinning down in the temporal quadrant of the cannabis users in comparison to the control group (p=0.022) (Table 1).

Comparison of the mean macular GCL-IPL thickness in the superior, superotemporal, inferotemporal, inferior, inferonasal and inferotemporal quadrants of the two groups indicated a statistically significant thinning in the superior and superotemporal quadrants of the cannabis users (p=0.006, p=0.027) (Table 2).

There was not a statistically sifnificant correlation between the duration of cannabis use and the RNF and GCL-IPL thicknesses of the cannabis users (p>0.05).

DISCUSSION

Many imaging studies, conducted to demonstrate the effects of cannabis use on brain morphology, demonstrated that

regular use of cannabis caused neuro-anatomical alterations in multiple brain regions (Chye et al. 2019, Scott et al. 2019). In particular, the most consistent result was decreased grey matter volume in the orbitofrontal cortex and the hippocampus, which are the key centers of the reward, motivation and learning circuits also affected in other substance use disorders (Lorenzetti et al. 2019a).

Demonstration of structural and functional alterations in the retina and optic nerve as parts of the central nervous system in many neurodegenerative diseases, has caused us to query effects on the retina and optic nerve of cannabis, already known to affect the central nervous system; and it has been aimed in this study to compare the OCT parameters of cannabis users and a control group. To the best of our knowledge, our study, is the first on this subject and has demonstrated a statistically significant thinning of the RNFL in the temporal quadrant in cannabis users. When we evaluated the thickness values of the GCL-IPL consisting of ganglion cell bodies and dendrites, significant thinning was found in the superior and superotemporal quadrants in cannabis users. These findings suggest that the effect of cannabis use is marked in the temporal region of the ganglion cell complex and in the retinal nerve fiber layer which is its continuation. There are few studies using OCT in psychiatric patients which mainly focused on schizophrenia and bipolar disorder and show that thinning occurs in the RNFL and GCC layers in parallel with the decrease in grey matter in bipolar disorder and schizophrenia (Celik et al. 2016, Garcia-Martin et al. 2018). The RNFL, formed by the ganglion cells, and the ganglion cell layer projecting to the lateral geniculate nucleus of the thalamus after forming the optic nerve, provides input for the visual cortex. An axonal damage at any point on this pathway causes retrograde transsynaptic axonal degeneratiton (RTAD), ultimately leading to atrophy in internal retinal layers such as the RNFL and ganglion cell layer (Petzold et al. 2016). Lizano et al. (2019) showed in their meta-analysis that cases with schizophrenia and bipolar disorder had significant thinning in RNFL and GCL-IPL compared to the control group and emphasized that this could occur via retrograde transsynaptic degeneration due to the pathophysiological damage in the thalamus and/or its projections the cerebellum, striatum and cerebral cortex.

Endogenous or exogenous cannabinoids regulate GABA release via CB1 receptors in the cerebral cortex. Chronic cannabinoid administration may lead to an imbalance in the stimulator and suppressor system by causing downregulation of the CB1 receptors in both animals and humans (Cheng at al. 2014). This may explain the cannabis-associated toxicity and structural changes in the brain demonstrated in many studies (Cheng et al. 2014, Hoffman at al. 2007). Moreover, these changes occurring in specific regions in the brain are known to correlate with the frequency of cannabis use (Lorenzetti et al. 2019b).

In conclusion, the results of our current study show that there may be an association between cannabis use and the degeneration in the retinal neural plexus. These patients have thinning in the RNFL, GCL-IP. OCT can be used to evaluate the volumetric decrease and damage in the central nervous system of cannabis users. Moreover, OCT may be useful for showing and monitoring neurodegeneration.

Limitations of the Study

Inclusion of limited number of cannabis using participants and the cross sectional design of the study are its primary limitations. Also, information on a standard dose administration could not be obtained since the patients expressed their daily habits of cannabis use in different ways. A gender based comparison was not possible as the cannabis using participants who attended the psychiatry outpatient clinic under probation between January 2016 and April 2016 were all male. Tobacco use by the participants was not queried. Longitudinal studies with larger patient groups may provide more robust results on the structural changes in the retina caused by cannabis.

REFERENCES

Adamson SJ, Sellman JD (2003) A prototype screening instrument for cannabis use disorder: the Cannabis Use Disorders Identification Test (CUDIT) in an alcohol-dependent clinical sample. Drug Alcohol Rev 22: 309-15

Celik M, Kalenderoglu A, Karadag AS et al (2016) Decreases in ganglion cell layer and inner plexiform layer volumes correlate better with disease severity in schizophrenia patients than retinal nerve fiber layer thickness: Findings from spectral optic coherence tomography. Eur Psychiatry 32: 9-15

Cheng H, Skosnik P, Pruce B et al (2014) Resting state functional magnetic resonance imaging reveals distinct brain activity in heavy cannabis users–a multi-voxel pattern analysis. J Psychopharmacol 28: 1030-40

Chye Y, Solowij N, Ganella EP et al (2017) Role of orbitofrontal sulcogyral pattern on lifetime cannabis use and depressive symptoms. Prog Neuropsychopharmacol Biol Psychiatry 79: 392-400

Chye Y, Suo C, Lorenzetti V et al (2019) Cortical surface morphology in long-term cannabis users: A multi-site MRI study. Eur Neuropsychopharmacol 29: 257-65

Downer E, Boland B, Fogarty M et al (2001) Δ9-Tetrahydrocannabinol induces the apoptotic pathway in cultured cortical neurones via activation of the CB1 receptor. Neuroreport 12: 3973-8

Fridberg DJ, Queller S, Ahn W-Y et al (2010) Cognitive mechanisms underlying risky decision-making in chronic cannabis users. J Math Psychol 54: 28-38

Garcia-Martin E, Gavin A, Garcia-Campayo J et al (2018) Visual function and retinal changes in patients with bipolar disorder. Retina (Philadelphia, Pa.)

Garcia-Martin E, Satue M, Otin S et al (2014) Retina measurements for diagnosis of Parkinson disease. Retina 34: 971-80

Hoffman AF, Oz M, Yang R et al (2007) Opposing actions of chronic Δ9-tetrahydrocannabinol and cannabinoid antagonists on hippocampal long-term potentiation. Learn Mem 14: 63-74

Kalenderoglu A, Sevgi-Karadag A, Celik M et al (2016) Can the retinal ganglion cell layer (GCL) volume be a new marker to detect neurodegeneration in bipolar disorder? Compr Psychiatry 67: 66-72

Khalil MA, Saleh AA, Gohar SM et al (2017) Optical coherence tomography findings in patients with bipolar disorder. J Affect Disord 218: 115-22

Lee WW, Tajunisah I, Sharmilla K et al (2013) Retinal nerve fiber layer structure abnormalities in schizophrenia and its relationship to disease state: evidence from optical coherence tomography. Invest Ophthalmol Vis Sci 54: 7785-92

Lizano P, Bannai D, Lutz O et al (2019) A Meta-analysis of Retinal Cytoarchitectural Abnormalities in Schizophrenia and Bipolar Disorder. Schizophr Bull 21 May 2019. pii: sbz029. doi: 10.1093/schbul/sbz029. [Epub ahead of print] PubMed PMID: 31112601.

Lorenzetti V, Chye Y, Silva P et al (2019a) Does regular cannabis use affect neuroanatomy? An updated systematic review and meta-analysis of structural neuroimaging studies. Eur Arch Psychiatry Clin Neurosci 269: 59-71

Lorenzetti V, Chye Y, Suo C et al (2019b) Neuroanatomical alterations in people with high and low cannabis dependence. Aust N Z J Psychiatry 12 Jul 2019: 4867419859077. doi: 10.1177/0004867419859077. [Epub ahead of print] PubMed PMID: 31298035.

Lowe DJ, Sasiadek JD, Coles AS et al 2019. Cannabis and mental illness: a review. Eur Arch Psychiatry Clin Neurosci 269: 107-20

Mehraban A, Samimi SM, Entezari M et al (2016) Peripapillary retinal nerve fiber layer thickness in bipolar disorder. Graefes Arch Clin Exp Ophthalmol 254: 365-71

Méndez-Gómez JL, Pelletier A, Rougier M-B et al (2018) Association of Retinal Nerve Fiber Layer Thickness With Brain Alterations in the Visual and Limbic Networks in Elderly Adults Without Dementia. JAMA Netw Open 1: e184406-e06

Mutlu U, Colijn JM, Ikram MA et al (2018) Association of retinal neurodegeneration on optical coherence tomography with dementia: a population-based study. JAMA Neurol 75: 1256-63

Petzold A, Wong S, Plant GT (2016) Autoimmunity in visual loss. In Handb Clin Neurol 133: 353-76

Scott JC, Rosen AF, Moore TM et al (2019) Cannabis use in youth is associated with limited alterations in brain structure. Neuropsychopharmacology 44: 1362

Sewell RA, Skosnik PD, Garcia-Sosa I et al (2010) Behavioral, cognitive and psychophysiological effects of cannabinoids: relevance to psychosis and schizophrenia. Braz J Psychiatry 32: 515-30.