Macula and Optic Disc Characteristics in Methamphetamine and Crystal Methamphetamine Abusers Using Optical Coherence Tomography

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Abstract

Purpose

Methamphetamine and Crystal Methamphetamine abusers were compared with healthy subjects using optical coherence tomography to assess their retinal nerve fiber layer, macula, and optic disc characteristics.

Methods

Forty-one Methamphetamine and Crystal Methamphetamine abusers and 42 healthy subjects (mean $\pm$ SD of age: 35.82 ± 8.6 and 37.67 ± 9.1 years, respectively) were incorporated in this cross sectional study. The drug abusers had a history of at least five years of substance use through smoking. Fourier-domain optical coherence tomography was used to image and assess the characteristics of retinal nerve fiber layer, macular thickness, and optic disc in the study groups.

Results

The retinal nerve fiber layer thickness was significantly lower in the superior and temporal retinal quadrants of drug abusers than healthy subjects ($P = 0.008$ and $P = 0.028$, respectively). This study did not find a significant difference between drug abusers and healthy controls regarding optic to disc ratio, rim area, and disc area ($P > 0.05$). The comparison between the study groups showed that the reductions in peripolea and the superior quadrant of parafoveal thickness were statistically significant ($P < 0.001$ and $P = 0.029$, respectively).

Conclusion

Fourier-domain optical coherence tomography measurements showed that the retinal nerve fiber layer and macular thickness were different between Methamphetamine and Crystal Methamphetamine abusers and healthy subjects, which should be considered in clinical practice. It seems that these drug abuses can cause alterations in retinal morphology.

Introduction

Methamphetamine (Meth) and Crystal Methamphetamine (Crystal Meth) are synthetic psychoactive substances belonging to the amphetamine class. There are sympathomimetic drugs that have a wide range of effects on the central nervous system. Meth and Crystal Meth stimulate the central nervous system by releasing monoamine neurotransmitters, including dopamine, norepinephrine, and serotonin [1–3]. These highly addictive substances can be taken by oral ingestion, nasal inhalation, intravenous injection, and smoking; however, the most common route of administration is smoking [4]. Because of

their euphoric properties, ease of synthesis, and easy availability, Meth and Crystal Meth abuse rates have widely increased worldwide. Consequently, current rates of abuse and dependences, the burden of care, side effects, and complications of these drugs have become a worldwide public health crisis [1, 5, 6]. Importantly, cardiovascular, respiratory, cerebrovascular, neurotoxic, and neurocognitive deficits, as well as psychosis, suicide, and premature death, are some of the physical and mental health problems following Meth and Crystal Meth use [7–9].

Ocular complications associated with Meth and Crystal Meth abuse include retinal vasculitis, endophthalmitis, episcleritis, panophthalmitis, scleritis, corneal ulceration, retinopathy, and transient visual losses [10, 11]. The majority of reports on Meth-induced retinal complications are animal experimental studies or rare case reports [10, 12]. Therefore, the *in vivo* assessment of retinal characteristics in humans with long-term Meth and Crystal Meth abuses is important for clinical purposes. To the best of our knowledge, there have been few reports on the impact of Meth and Crystal Meth on retinal nerve fiber layer (RNFL) characteristics, macular thickness, and optic nerve head (ONH) features. Only in a recent study, Talebnejad et al. evaluated RNFL thickness without investigation of the fovea, perifovea and parafovea features in Meth abusers and found an adverse association with RNFL thickness using optical coherence tomography (OCT) modality [12]. OCT is an imaging technique that enables non-contact direct observation and high-resolution cross-sectional images of the retinal tissue and ONH in a noninvasive manner. It provides *in vivo* measurements of macula characteristics, optic disc features, and RNFL thickness. Fourier-domain OCT represents a modification of the OCT system and is capable of accurate and high-speed imaging of the retina [13].

While the effects of Meth and Crystal Meth abuses on the retina have been reported in experimental animal studies or case reports [10, 14–17], it seems necessary to design a study that can assess the impact of Meth and Crystal Meth-induced retinal changes in chronic drug abusers as compared to the results with retinal characteristics of healthy subjects. Therefore, this study was designed to evaluate RNFL, ONH, and macula characteristics in long-term Meth and Crystal Meth abusers and compare them with healthy subjects using a Fourier-domain OCT.

Methods

This cross-sectional study was conducted at Al-Zahra Eye Hospital, Zahedan, eastern Iran. All participants in this study were residents of Zahedan with the same ethnicity.

The study was approved by the Institutional Review Board/Ethics Committee of Zahedan University of Medical Sciences (Code ID: IR.ZAUMS.REC.1398.431). The procedures performed in this study were based on the principles of the Declaration of Helsinki. The participants received information about the study and written informed consent forms were signed by them.

Initially, Meth and Crystal Meth addicts were identified from the camp protected by Zahedan Health Center. The participants received a comprehensive ophthalmic examination, including full patient history, slit-lamp biomicroscopy, ophthalmoscopy, noncontact tonometry (Topcon CT-1/CT-1P, Tokyo, Japan),

autorefraction (Topcon KR-1, Tokyo, Japan), and best-corrected distance visual acuity. A refractive error between - 3.00 to + 3.00 diopters with a best-corrected distance visual acuity of 0.2 Log MAR was added to the inclusion criteria to avoid the manifestations of high refractive errors on the retina [18]. The exclusion criteria for both study groups involved any systemic or ocular disease, history of ocular surgery, and consumption of a specific drug. Also, women who were currently pregnant were excluded.

Considering the mentioned criteria, 41 Meth and Crystal Meth abusers with at least 5 years of Meth and Crystal Meth abuse were enrolled in this study. Notably, the route of Meth and Crystal Meth usage was smoking with a mean daily dose of 0.0074 ± 0.0034 gr. Forty-two healthy individuals of matching ethnicity to the addicted group and without a history of smoking were included in the study as the control group.

RNFL, ONH, and macula images of the participants were obtained using a Fourier-domain OCT (Optovue, RTVue™, Inc., Fremont, CA), which is the first United States Food and Drug Administration-approved FD-OCT system. Optovue Fourier-domain OCT system can take 26,000 A-scans per second with an axial resolution of 5 microns using a high wavelength light source. This technique utilizes a superluminescent diode that is compact, reliable, and more economical [13]. Repeatability of RNFL and macular thickness measurements have been studied in previous studies using Optovue Fourier-domain OCT [19, 20]. This device allows for automatic and manual imaging by the clinician. In this study, the manual imaging technique was used to examine RNFL, ONH, and macular thickness. The same examiner (M.M) obtained all OCT measurements based on the manufacturers' user guide and previous studies [21]. Measurements based on the quality state provided by the instrument were accepted and erroneous captures were repeated after five minutes. It should be mentioned that the mechanism of the RTVue OCT has been described in previous studies [21, 22]. The manufacturer's representative checked the calibration of OCT before the study. Lastly, only the right eye per subject was selected for analysis.

RNFL Measurements

The ONH protocol was used to obtain RNFL measurements. This protocol generates an RNFL thickness map measured along a circle of 3.45 mm in diameter centered at the ONH. The overall average, superior hemisphere, inferior hemisphere, temporal quadrant, superior quadrant, nasal quadrant, and inferior quadrant are provided [21, 22].

ONH Measurements

The ONH protocol was used to obtain ONH measurements. It consists of 12 radial scans of 3.4 mm in length (455 A-scans each) and 13 concentric circular scans ranging from 1.3 to 4.9 mm in diameter (425–965 A-scans each) centered at the ONH. The ONH parameters measured by the software involved the rim area, vertical cup-to-disc ratio, horizontal cup-to-disc ratio, cup area, cup-to-disc area ratio, and disc area [22].

Macular Measurements: The ganglion cell complex (GCC) protocol was used to obtain macular measurements. This protocol consists of one horizontal line scan of 7 mm in length (467 A-scans) followed by 15 vertical line scans of 7 mm in length (400 A-scans each) at 0.55-mm intervals. This protocol provides 14,810 A-scans in 0.58 seconds of a rectangular area. The GCC protocol provides a segmentation of macular B-scans in two layers: GCC layer and outer retinal layer. The GCC layer is composed of the ganglion cell layer, the nerve fiber layer, and the inner plexiform layer [22].

Statistical analysis was performed using the SPSS program (SPSS version 19 for Windows; SPSS Inc., Chicago, IL, USA). The normality of data distribution was assessed using the Kolmogorov-Smirnov test. The independent T-test was utilized to compare the mean of the studied variables in addict and healthy groups. The descriptive results of comparisons are presented using the mean and 95% confidence interval of differences. In this study, *P*-values smaller than 0.05 were considered significant.

Results

Forty-one eyes of 41 Meth and Crystal Meth abusers (36 males and 5 females) and 42 eyes of 42 healthy individuals (34 males and 8 females) were enrolled in this study. The age means of the drug abusers and healthy subjects were 35.82 ± 8.6 years and 37.67 ± 9.1 years, respectively. No significant differences were found between the two groups in sex and age ($P = 0.326$ and $P = 0.397$, respectively). There were no significant differences in refractive errors and RNFL and macula features between the two eyes ($P > 0.05$). Therefore, statistical analysis was performed only for the right eye of all participants

The mean of spherical equivalent refractive errors in the two groups were -0.47 ± 1.68 diopter and -0.70 ± 0.98 diopter, respectively. There were no significant differences in refractive errors between drug abusers and healthy subjects ($P = 0.496$).

The results of the independent T-test showed significant differences in RNFL thickness between the two groups in superior and temporal quadrants (-6.65 , 95% CI: $-11.49, -1.08$, $P = 0.008$ and -4.65 , 95% CI: $-8.81, -0.50$, $P = 0.028$, respectively) (Table 1). Examination of RNFL thickness showed no statistically significant difference in other quadrants, namely, inferior and nasal, between drug abusers and healthy subjects ($P = 0.346$ and $P = 0.696$, respectively).

Table 1
Retinal nerve fiber layer thickness in Methamphetamine and Crystal Methamphetamine abusers and healthy subjects

	Drug abusers Mean $\pm$ SD	Healthy subjects Mean $\pm$ SD	<i>P</i> -value
Superior hemisphere	101.24 $\pm$ 9.52	106.19 $\pm$ 7.61	0.011
Inferior hemisphere	99.73 $\pm$ 10.41	101.16 $\pm$ 7.15	0.466
Superior	120.68 $\pm$ 12.05	127.33 $\pm$ 10.05	0.008
Inferior	125.63 $\pm$ 12.86	128.07 $\pm$ 10.47	0.346
Temporal	74.31 $\pm$ 11.99	78.97 $\pm$ 6.19	0.028
Nasal	81.26 $\pm$ 12.05	80.33 $\pm$ 9.51	0.696
Overall NFL thickness	100.58 $\pm$ 9.46	103.66 $\pm$ 6.50	0.087
SD: Standard deviation, NFL: Nerve fiber layer, Unit of the parameters is micron (μm), Statistically significant <i>P</i> -value is bolded.			

A comparison of ONH features measured by the OCT between the two groups is presented in Table 2. The results showed approximately similar values in the two groups. The difference in optic disc ratio (total, vertical, and horizontal), rim area, and disc area was not statistically significant between drug abusers and healthy subjects ($P > 0.05$).

Table 2
Optic nerve head features in Methamphetamine and Crystal Methamphetamine abusers and healthy subjects

	Drug abusers Mean $\pm$ SD	Healthy subjects Mean $\pm$ SD	<i>P</i> -value
Cup-to-disc ratio	0.29 $\pm$ 0.13	0.29 $\pm$ 0.14	0.813
Cup-to-disc vertical ratio	0.48 $\pm$ 0.14	0.48 $\pm$ 0.16	0.946
Cup-to-disc horizontal ratio	0.56 $\pm$ 0.17	0.60 $\pm$ 0.23	0.467
Rim area	1.43 $\pm$ 0.27	1.44 $\pm$ 0.29	0.863
Disc area	2.05 $\pm$ 0.36	2.08 $\pm$ 0.26	0.736
SD: Standard deviation, Statistically significant <i>P</i> -value is bolded, Unit of Rim area and disc area is in square millimeters (mm^2).			

Table 3 demonstrates the macular characteristics of the drug abusers and healthy subjects. The results showed a statistically significant reduction in perifovea thickness and its quadrants in the drug abusers compared to healthy subjects ($P < 0.001$). Compared with healthy subjects, a statistically significant

reduction was found in the superior parafoveal quadrant in the drug abusers (-5.79, 95% CI: -10.97, -0.60, $P=0.029$).

Table 3
Macular thickness profiles in Methamphetamine and Crystal Methamphetamine abusers and healthy subjects

	Drug abusers Mean $\pm$ SD	Healthy subjects Mean $\pm$ SD	<i>P</i> -value
Parafovea thickness	313.00 $\pm$ 15.68	318.04 $\pm$ 11.85	0.101
Superior hemisphere parafovea	312.78 $\pm$ 14.36	317.85 $\pm$ 9.49	0.060
Inferior hemisphere parafovea	313.14 $\pm$ 17.31	316.80 $\pm$ 11.15	0.254
Superior parafovea	315.70 $\pm$ 13.52	321.50 $\pm$ 10.01	0.029
Inferior parafovea	314.82 $\pm$ 17.71	318.42 $\pm$ 12.05	0.281
Temporal parafovea	304.36 $\pm$ 16.27	308.61 $\pm$ 10.18	0.156
Nasal parafovea	317.34 $\pm$ 17.09	320.80 $\pm$ 10.68	0.270
Perifovea thickness	281.24 $\pm$ 13.43	290.47 $\pm$ 12.08	0.001
Superior hemisphere Perifovea	282.80 $\pm$ 12.46	293.09 $\pm$ 12.51	< 0.001
Inferior hemisphere perifovea	279.68 $\pm$ 14.76	287.90 $\pm$ 12.26	0.007
Superior perifovea	281.82 $\pm$ 13.22	292.19 $\pm$ 13.53	0.001
Inferior perifovea	274.82 $\pm$ 15.05	282.69 $\pm$ 12.86	0.012
Temporal perifovea	272.58 $\pm$ 13.43	280.26 $\pm$ 11.56	0.007
Nasal perifovea	295.46 $\pm$ 14.61	306.90 $\pm$ 13.82	< 0.001
SD: Standard deviation, Unit of the parameters is micron (μm), Statistically significant <i>P</i> -value is bolded.			

Pearson correlation test showed a significant relationship between decreased thickness of RNFL and perifovea with duration of Meth and Crystal Meth abuse (perifovea thickness: $P=0.006$, $r=-0.297$, RNFL thickness in superior quadrant: $P=0.004$, $r=-0.310$, RNFL thickness in temporal quadrant: $P=0.025$, $r=-0.246$).

Discussion

The main cause of Meth and Crystal Meth-related disorder in humans and laboratory animals has been attributed to central nervous system stimulation and sympathomimetic effects on peripheral adrenergic structures [23]. Moreover, there are numerous reports of ocular sequel associated with using these drugs

[10, 11]. The present study evaluated the characteristics of the macula, RNFL, and ONH in Meth and Crystal Meth abusers with a minimum five-year history of their abuse.

According to the results of this study, long-term Meth and Crystal Meth abuses had a significant impact on RNFL thickness in superior and temporal quadrants. In addition, a statistically significant decline in perfovea and superior parafovea thickness was observed in the drug abusers group as compared to healthy controls. In contrast, cup-to-disc ratio, rim area, and disc area were similar between the drug abusers and healthy subjects.

Concerning the effects of long-term Meth and Crystal Meth abuse on RNFL thickness, the results of the present study showed a significant reduction in the thickness of RNFL, that this decrease was greater with increasing the duration of drug addiction. The result of this study is consistent with the findings of a study by Talebnejad et al [12]. As they have noted, RNFL thickness showed a significant reduction in Meth abusers compared to the healthy group [12]. Gemelli et al. also reported that the average RNFL thickness in the cocaine users was significantly thinner compared to that of healthy subjects [24]. It should be mentioned that cocaine is a psycho-stimulant drug with a similar function to Meth. A suggested mechanism for the decreased RNFL thickness in drug abusers involves neural damage caused by microvascular alterations and oxidative stress induced by long-term abuse, which might lead to the development of retinal microstructural changes [25, 26].

Interestingly, Meth and cocaine-induced topographic changes of RNFL differ from study to study. Talebnejad et al. demonstrated thinner RNFL thickness in temporal, superior temporal, and inferior nasal areas in Meth users compared to healthy subjects [12], while Gemelli et al. observed an RNFL thinning due to cocaine consumption in the superior, inferior, and nasal quadrants [24]. On the other hand, our results showed RNFL thinning in the superior and temporal quadrants. Given that RNFL thinning in each quadrant helps differentiate some ocular diseases such as glaucoma and neuro-ophthalmic disorders from normal conditions [12], a new RNFL thickness threshold seems to be needed for Meth and Crystal Meth abusers.

There are scarce studies that have investigated the effects of chronic Meth and Crystal Meth consumption on macular thickness by using Fourier-domain OCT. The results of the current study demonstrated that Meth and Crystal Meth abusers have a decreased perfovea (all quadrants) and superior parafovea thickness compared to healthy controls. Given that macula is supplied by a dual circulation, these findings could be attributed to the retinal ischemia secondary to vasospasm of the choroidal capillary due to a sympathetic effect of the drugs [2, 27]. Two cases of bilateral acute macular neuroretinopathy following intranasal cocaine use have been reported by Introni et al [27]. It seems that ischemia of the deep capillary plexus is the cause of early outer plexiform layer lesions in macular neuroretinopathy [28]. However, Gemelli et al. have reported no significant differences in macular thickness in cocaine users in comparison to the control group [24]. Compared with other studies reporting the impact of cocaine on macular thickness [24], the present study is the first report of the effects of chronic Meth and Crystal Meth abuse on the macular thickness profile using Fourier-domain OCT.

One of the limitations of this study is that the study did not evaluate vascular problems associated with the consumption of drugs. It is suggested that further research be conducted to evaluate vascular problems associated with the consumption of drugs using OCT angiography of the optic nerve.

Conclusion

This study revealed that chronic Meth and Crystal Meth abuse can have significant effects on RNFL and perfovea thickness. Statistically significant RNFL thickness reductions were observed in the superior and temporal quadrants and perfovea and superior parafovea thickness of Meth and Crystal Meth abusers compared to healthy subjects. Clinicians can use these findings in their clinical approaches towards these patients.

Declarations

Acknowledgment

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Conflicts of interest

None of the authors has any conflicting interests to disclose.

Competing Interests:

My coauthors and I do not have any interests that might be interpreted as influencing the research and medical ethics were followed in the conduct of the study.

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No funding was received for conducting this study.

Author contribution:

All authors have had their share of the work, have been involved in preparation of the manuscript and have approved the submitted version.

Data Availability:

The data is available and will be sent if needed.

Animal Research (Ethics):

This study was not an animal research.

Consent to Participate (Ethics):

The participants received information about the study and written informed consent forms were signed by them.

Consent to Publish (Ethics):

All of the authors listed in the byline have agreed to the byline order and to submission of the manuscript in this form.

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