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Degenerative brain changes associated with tramadol use: an optical coherence tomography study

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Abstract

Background Tramadol—a synthetic opioid originally used as an analgesic—has been widely misused as an addictive drug in the middle east in the last twenty years. Brain changes associated with long-term tramadol use are understudied. This study aimed to detect the possible effects of tramadol use for at least one year on the brain. Optical coherence tomography (OCT) as a noninvasive measure can assess changes in retinal thickness which reflects degenerative changes in the brain.

Methods Twenty-five patients fulfilling the tramadol use disorder according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria were compared to 25 matched control subjects free of substance use disorders. Other psychiatric and medical conditions that may affect OCT were excluded from both groups. Patients were assessed using Addiction Severity Index; meanwhile, both groups were evaluated using OCT.

Results Patients with tramadol use showed a lower thickness of most OCT parameters than healthy non-tramadol controls. The retinal nerve fiber layer (RNFL) thickness was not associated with tramadol dose, duration of use, or the age of first use. There were differences between the right and left eyes in RNFL and Ganglion cell complex (GCC) thickness.

Conclusions Long-term tramadol use is associated with decreased thickness of RNFL that can be a potential marker and an early sign for degeneration detected by noninvasive techniques like OCT.

Keywords Tramadol, OCT, RNFL, GCC, Opiates

Introduction

Tramadol is a centrally acting synthetic analgesic with agonist action on μ-opioid receptors. Besides, it acts as an agonist on serotonin and norepinephrine, like serotonin-norepinephrine reuptake inhibitors (SNRI) [1, 2]. Tramadol, as an addictive drug, has emerged over the past 20 years as a significant public health problem in Egypt and other Middle Eastern countries [3–5]. Other countries in Europe and Asia reported abuse of tramadol as an addictive drug [6, 7]. Patients prefer it as it has mixed actions as an analgesic, a stimulant, an antidepressant effect, and a treatment for premature ejaculation [1, 8–10]. In contrast with heroin, pleasure-seeking was found to be a more powerful motive to use tramadol rather than pain avoidance [11].

Many studies have reported psychiatric complications associated with tramadol use. Cognitive impairment, manic symptoms, psychotic symptoms, and anxiety

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symptoms are tramadol users' most common psychiatric symptoms [9, 12–16].

Long-term tramadol use was also linked to neurological disorders such as seizures and degenerative conditions like Alzheimer's and Parkinson's [17]. However, only a few studies examined the effect of tramadol on the brain. The effect of tramadol on structural brain changes was detected in animal studies [18, 19]. Magnetic resonance imaging (MRI) found no significant structural brain changes in patients with tramadol poisoning by magnetic resonance imaging (MRI). Layegh and Ghorbanpour [20] found that some tramadol patients (8 out of 15 patients examined) had hyper signal foci in the white matter in MRI imaging compared to the control group. However, no specific pattern could be detected in such lesions. Enhancement of the reward system, including the nucleus accumbens in the functional MRI, was reported after tramadol intake [21].

The shortage of information about brain changes in tramadol users increases the importance of using a simple, noninvasive method to study these possible changes.

The retina contains several layers of non-myelinated neurons originating from the brain and includes axons and glia interconnected by synapses. Optical coherence tomography (OCT) is a noninvasive and relatively short-duration technique with high-resolution, cross-sectional retina images and automatic measurement of retinal and nerve fiber layer thickness [22]. OCT can be considered a window to follow neurodegenerative changes in the brain using a simple, noninvasive procedure [23]. Although it is an optical analog of ultrasound B-mode imaging, OCT differs from ultrasound waves as direct detection of light echoes is not possible in OCT because the speed of light is much faster than the speed of sound. With OCT, high-resolution cross-sectional or 3-dimensional images of the internal retinal structure are generated by an optical beam being scanned across the retina and the magnitude and echo time delay of backscattered light being measured [24].

Important structures of the inner part of the retina include retinal nerve fiber layer thickness (RNFL), ganglion cell complex (GCC), and inner plexiform layer (IPL). RNFL consists of non-myelinated axons of the ganglion cells which courses along the inner part of the retina and aggregates to form the optic nerve extending to form the optic chiasma and optic tract. GCC, on the other hand, consists of bodies of the ganglion cells; nerve fiber layer and IPL are the dendrites of ganglion cells [25]. Peripapillary RNFL decreased thickness is related to neuron loss and axonal loss. Being non-myelinated, RNFL is considered a more sensitive and noninvasive parameter for evaluating degeneration changes in the brain in neurological diseases like multiple sclerosis [26, 27]. The RNFL is the best brain structure candidate for visualizing the processes of neurodegeneration, neuroprotection, and, potentially, even neuro-repair. OCT can view high-resolution reconstructions of retinal anatomy rapidly and permits objective analysis of the RNFL (axons) as well as ganglion cells and other neurons in the macula [24].

OCT has previously been used in psychiatric disorders to examine brain degenerative changes. Patients with schizophrenia, depression, bipolar disorder, and obsessive–compulsive disorder have shown different RNFL and GCC changes [28–31]. RNFL and GCC thickness was reduced in the patients with schizophrenia compared with the controls [32]. Also patients with bipolar disorder had showed thinning in the retinal nerve fibers detected by OCT [29]. OCD patients had progressive decrease in RNFL thickness with longer duration of their OCD duration [33]. Patients with MDD did not show significant differences in OCT findings compared to controls [34].

Changes in the retinas of patients with substance use disorders were detected with OCT. Patients using alcohol, cannabis, cocaine, methamphetamines, and opiates showed different RNFL thickness changes [32, 35–39]. Patient with opioid dependence had significantly thinner RNFL than controls [36]. Orum et al. found that patients with alcohol use show decrease in retinal fiber layers in comparison to non-alcoholic, and this decrease is associated with duration of alcohol use [35]. Similar thinning of the RNFL layers were reported in cocaine and cannabis users [38, 40].

According to our knowledge, no other previous studies have examined patients with tramadol use with OCT. Moreover, two studies have only studied the possible structural changes in the brains of tramadol users using MRI [20, 21]. Accordingly, this study would add new information about the brain effects of using tramadol.

This study aimed to detect the effect of long-term use of tramadol on the retina—and hence the brain—in patients with tramadol use disorders using OCT as a noninvasive measure. We hypothesized that long-term use of tramadol would be associated with changes in OCT parameters in tramadol use patients in comparison to controls.

Methods

Participants

This study was an observational analytic case–control study with a convenient sample. Twenty-five patients with tramadol use disorder were recruited consecutively from the Psychiatry and Addiction Hospital of Cairo University outpatient clinic. Patients were 18–40 years old, males and females, fulfilling the tramadol use disorder criteria according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [41] for at least one year. In the literature, prolonged opioid use was

considered a nine-month use without medical indication [42]; meanwhile, we extended the long-term tramadol use to be not less than one year to guard against the effect of recall bias by the patients.

Patients with schizophrenia, bipolar disorder, major depression, or any other psychiatric were excluded. Patients with ocular or systemic pathologies that could affect the OCT findings (including errors with the spherical equivalent of ≥ 6 diopters (both myopic and hyperopic), hypertension, diabetes mellitus, glaucoma, ocular hypertension, and multiple sclerosis) were also excluded. Patients above forty were excluded to decrease the possibility of degenerative brain changes. Besides, most of patients seeking treatment in the outpatient clinic were younger than 40. Infrequent use of other substances—according to the ASI and DSM-5 criteria—was not an exclusion criterion unless the patient fulfills the criteria of use for this substance according to DSM-5.

The second group included 25 control subjects consisted of healthy controls who matched the patients in age and sex and were free of any substance use disorders, psychiatric disorders, neurological disorders, or other medical disorders that may affect OCT findings.

Psychiatric assessment

The Addiction Severity Index (ASI) [43] provided a multidimensional assessment of substance use in the patient group. It is a semi-structured interview composed of seven sections that evaluate medical complications, employment, alcohol and drug use, and legal, family/social, and psychiatric problems. Each section's severity ratings (0–9) reflect how the interviewer believes the patient needs additional treatment. The severity ratings are interviewer estimates of the patient's need for additional treatment in each area. The scales range from 0 (no treatment necessary) to 9 (treatment needed to intervene in life-threatening situations). Each rating is based upon the patient's history of problem symptoms, present condition, and subjective assessment of his treatment needs in a given area. The following is a general guideline for the ratings:

0–1 No real problem, treatment not indicated.
2–3 Slight problem, treatment probably not necessary.
4–5 Moderate problem, some treatment indicated.
6–7 Considerable problem, treatment necessary.
8–9 Extreme problem, treatment absolutely necessary.

Detailed information about tramadol use, including onset, doses, route, intoxication, withdrawal, and medical complications was highlighted.

Diagnosis was confirmed using the DSM-5 criteria of substance use disorder applied by 2 consultant psychiatrists (the authors) who also applied the psychiatric assessment.

Ophthalmological assessment

Both groups were subjected to an ophthalmological assessment for OCT, including anterior segment examination by slit lamp, intraocular pressure measurement by Goldman applanation tonometry, fundus examination by indirect ophthalmoscopy, and slit-lamp biomicroscopy. Best-corrected visual acuity was done before optical coherence tomography.

All subjects had a retinal nerve fiber layer assessment using the RTVue spectral-domain OCT's glaucoma profile (Optovue Inc, Fremont, California, USA). The examination of each subject lasted 5–7 min. Before the OCT examination, mydriatic drops were applied to dilate the pupil to acquire the OCT images. The subject was then asked to position their head in the head mount and fixate on a target light inside the ocular lens (internal fixation). RNFL thickness map, optic nerve head analysis scans, and GCC thickness maps were obtained. RNFL thickness parameters (overall average, superior average, inferior average, and nasal and temporal averages) were recorded and analyzed.

The ophthalmological examination and the OCT assessment were done in the Laser Unit of the Ophthalmology Department, Kasr Al-Ainy hospitals by the two consultant ophthalmologists (authors).

The study protocol was approved by the Cairo University Research Ethics Committee (REC) under the number (N-16–2018) and conducted following the tenets of the Declaration of Helsinki. Patients and control subjects signed informed written consents before participation in the study.

Statistical analysis

Results were analyzed using Statistical Package for the Social Sciences (SPSS) 20 [44]. The Kolmogorov–Smirnov test tested the normality of data, and then data were described using frequency (percent) and mean ± SD. Mann–Whitney test was used to compare numerical data, while the Spearman correlation test was used for correlations. The Wilcoxon signed-rank test was used in the comparison of paired samples. *P* values less than 0.05 were considered statistically significant. The sample size calculation was done using G*Power software version 3.1.9.2. An effect size of 0.8 was detected in a prior study of OCT [45]. Power of 0.8 and α of 0.05 were considered to get a sample size of 26 subjects in each group. A group of 30 patients started the study, but only 25 completed the required examinations.

Results

Patients and control subjects were matched in age and sex (Table 1). The average dose of tramadol was (2748 ± 4346) mg per day. Patients started to take tramadol at the age of (18.44 ± 3.25) years old for (7.08 ± 3.53) years (Table 1).

RNFL thickness in patients was less than in controls in both eyes except the Rt GCC. The differences were significant in Rt RNFL total average ($p \leq 0.001$), Lt RNFL total average ($p \leq 0.001$), Lt RNFL superior ($p = 0.045$), Lt RNFL inferior ($p = 0.013$), and Lt GCC average ($p = 0.043$) (Table 1).

The correlation between OCT parameters and the age of patients, average tramadol dose, duration of tramadol use, and age at 1st tramadol use were not statistically significant (Table 2).

Comparison between right and left eyes in patients and controls revealed a significantly lower GCC average in left eyes ($p = 0.004$) in patients (Table 4) and a significantly higher GCC average in left eyes ($p = 0.033$) in controls (Table 3). At the same time, other parameters were lower in the left eyes, but the differences were not significant (Tables 3 and 4).

Discussion

Patients with tramadol use showed thinning of all RNFL and GCC measures compared to subjects in the control group except the Rt GCC. The difference was significant in all parameters of the left eyes and the average RNFL of the right eyes.

As the retina shares developmental, physiological, and anatomical features with the brain, retinal imaging is increasingly being used to study neurodegenerative diseases, and the direct relationship between RNFL thinning and cerebral atrophy has already been shown in many studies regarding neurological and psychiatric diseases. Thus, more thinning of the retinal layers would suggest more brain affection and probably more deterioration in the patient. Many studies investigated the effect of substance use on the OCT parameters, revealing conflicting results. To our knowledge, this is the first study investigating OCT changes in patients with tramadol use.

Kalenderoglu and Orum [32] found that RNFL thickness increased in patients with cannabis use and patients with multiple substance use compared to healthy controls. In contrast, another study reported decreased RNFL thickness in cannabis users [40].

Table 1 Demographics, substance data, and optical coherence tomography in patients with tramadol use and controls

		Patients with tramadol use disorder *N*: 25	Control subjects *N*: 25	*P* value
Age		26.20 ± 4.45	30.12 ± 8.16	0.124
Gender	Males	24/96%	21/84%	0.349
	Females	1/4%	4/16%	
Tramadol average dose (mg/day)		2748.00 ± 4346.00	X	X
Duration of tramadol use (years)		7.08 ± 3.53	X	X
Age at 1st tramadol use (years)		18.44 ± 3.25	X	X
Addiction severity index	Medical	1.92 ± 1.93	X	X
	Employment	7.08 ± 0.99	X	X
	Drug use	7.40 ± 0.50	X	X
	Legal	5.16 ± 2.61	X	X
	Family history	0.72 ± 0.46	X	X
	Family status	6.64 ± 1.11	X	X
	Psychiatric problems	2.52 ± 2.06	X	X
Optical coherence tomography	Rt RNFL average µm	110.82 ± 10.80	121.96 ± 4.38	*< 0.001*
	Rt RNFL superior µm	110.48 ± 10.98	112.20 ± 11.23	0.594
	Rt RNFL inferior µm	110.48 ± 12.65	117.23 ± 23.68	0.554
	Rt GCC average µm	99.87 ± 6.23	98.37 ± 8.042	0.244
	Lt RNFL average µm	107.80 ± 14.37	121.35 ± 4.06	*< 0.001*
	Lt RNFL superior µm	107.98 ± 15.48	119.53 ± 26.03	*0.045*
	Lt RNFL inferior µm	107.00 ± 16.42	120.23 ± 25.37	*0.013*
	Lt GCC average µm	95.51 ± 10.73	101.72 ± 8.87	*0.043*

RNFL retinal nerve fiber layer

GCC Ganglion cell complex

Table 2 Correlation between optical coherence tomography measures and clinical data in patients with tramadol use

N = 25			Optical coherence tomography							
			Rt RNFL average	Rt RNFL superior	Rt RNFL inferior	Rt GCC average	Lt RNFL average	Lt RNFL superior	Lt RNFL inferior	Lt GCC average
Age		**rs**	−0.036	0.243	−0.150	−0.092	−0.026	0.077	−0.012	0.291
		P	0.864	0.242	0.475	0.662	0.903	0.714	0.956	0.158
Tramadol average dose		**rs**	−0.256	−0.324	−0.120	0.107	−0.200	−0.256	0.018	−0.161
		P	0.217	0.114	0.568	0.611	0.337	0.217	0.931	0.443
Duration of tramadol use		**rs**	0.100	0.348	−0.025	−0.009	0.063	0.179	0.074	0.412
		P	0.633	0.088	0.905	0.967	0.764	0.392	0.724	0.041
Age at 1st tramadol use		**rs**	−0.043	0.092	−0.033	0.142	−0.073	−0.048	−0.013	0.142
		P	0.839	0.662	0.875	0.498	0.730	0.818	0.950	0.498
Addiction severity index	**Medical**	**rs**	−0.177	−0.257	−0.076	0.329	−0.235	−0.315	0.036	0.152
		P	0.398	0.215	0.720	0.109	0.259	0.125	0.865	0.467
	Employment	**rs**	−0.277	−0.071	−0.326	−0.112	*−0.406*	−0.254	−0.272	−0.144
		P	0.180	0.736	0.112	0.595	*0.044*	0.220	0.189	0.493
	Drug use	**rs**	0.136	0.159	0.079	-0.057	0.192	0.192	0.272	0.057
		P	0.517	0.449	0.706	0.788	0.357	0.357	0.189	0.788
	Legal	**rs**	−0.146	−0.057	−0.070	0.102	−0.243	−0.205	−0.118	−0.054
		P	0.486	0.788	0.739	0.626	0.242	0.326	0.574	0.797
	Family history	**rs**	−0.173	−0.111	−0.198	−0.247	0.074	0.136	−0.062	−0.272
		P	0.408	0.597	0.343	0.234	0.725	0.517	0.769	0.189
	Family status	**rs**	−0.085	0.135	−0.201	−0.198	0.017	0.160	−0.094	0.166
		P	0.685	0.520	0.335	0.342	0.937	0.445	0.654	0.428
	Psychiatric problems	**rs**	−0.007	0.154	−0.043	−0.272	0.044	0.078	0.157	0.134
		P	0.973	0.464	0.839	0.188	0.836	0.713	0.455	0.524

RNFL retinal nerve fiber layer

GCC ganglion cell complex

rs Spearman's rank correlation coefficient

Table 3 Comparison between right and left eyes of controls as regard retinal nerve fiber layer and ganglion cell complex

	Right eye *N: 25*	Left eye *N: 25*	*p* Value
RNFL average *μm*	121.96 ± 4.38	121.35 ± 4.06	0.523
RNFL superior *μm*	112.20 ± 11.23	119.53 ± 26.03	0.726
RNFL inferior *μm*	117.23 ± 23.68	120.23 ± 25.37	0.264
GCC average *μm*	98.37 ± 8.042	101.72 ± 8.87	*0.033*

RNFL retinal nerve fiber layer

GCC ganglion cell complex

Table 4 Comparison between right and left eyes of patients as regard retinal nerve fiber layer and ganglion cell complex

	Right eye *N: 25*	Left eye *N: 25*	*p* Value
RNFL average μm	110.82 ± 10.80	107.80 ± 14.37	0.166
RNFL superior μm	110.48 ± 10.98	107.98 ± 15.48	0.221
RNFL inferior μm	110.49 ± 12.65	108.00 ± 16.43	0.226
GCC average μm	99.87 ± 6.23	95.51 ± 10.73	*0.004*

RNFL retinal nerve fiber layer

GCC ganglion cell complex

Another study included patients with alcohol and tobacco dependency who had thinning in all quadrants of RNFL [37].

Methamphetamine users for more than five years showed decreased retinal nerve fiber layer thickness compared to the normal population [46]. Cocaine users in a small study (17 users) showed similar thinning of the nasal, superior, and inferior RNFL quadrants [38].

Conflicting results were obtained from studies that included OCT assessment in opiate users. One study examined patients with opiate use, reported relative thinning in the choroidal layer, and increased two quadrants of RNFL compared to normal subjects [35]. The study included male patients with acute opiate use only. Another study found differences between opiate-dependent patients and normal healthy subjects regarding RNFL thickness. A unilateral decrease in RNFL thickness in patients with opiate dependence was detected in 2 parameters [36]. A third study found no differences between opiate users and normal controls in any quadrant of both eyes [47].

Activation of opioid receptors was linked to a neuroprotective effect against ischemic insults to the retina [48, 49]. Meanwhile, the neurotoxic effects of opiates on the brain include chronic hypoxia, oxidative stress, and micro-DNA damage [50]. These findings may explain the thinning of RNFL in tramadol users via the tramadol effect as an opiate agonist.

The other neurotransmitters stimulated by tramadol may provide another explanation for RNFL thinning. Tramadol has similarities to the pharmacological effect of selective serotonin reuptake inhibitors (SSRIs) as both increase serotonin (Nakhaee et al., 2021). Increased serotonin by SSRIs was linked to decreased retinal GCC and RNFL thickness [51]. This increased serotonin may increase phospholipase C (PLC) activity, an enzyme that plays a critical role in retinal degeneration because of its relation to photoreceptor cell death [52, 53].

Vascular causes may also explain the retinal changes observed in patients with tramadol use. One of the complications of long-term tramadol use is hypertension. Hypertension is associated with the decreased thickness of RNFL [54, 55]. Moreover, thromboembolic lesions—including pulmonary embolism and myocardial infarction—were reported in patients using tramadol [56, 57].

In this study, tramadol dose, duration of use, and age of first use were not correlated with OCT parameters. The previously mentioned studies that assessed RNFL thickness did not associate RNFL thickness with substance doses, duration of use, or SSRIs [32, 35, 36, 38, 51]. The absence of this association may suggest that OCT changes can be considered trait markers rather than state markers of tramadol use. Further studies may confirm this conclusion, including current versus recovered tramadol users.

Patients' left eyes were thinner than the right ones in all parameters; however, the difference was only significant in the GCC average. Many studies reported conflicting results comparing RNFL parameters between the right and left eyes. A study [58] found increased RNFL of the superior quadrant in the left and temporal quadrant in the right eyes, while no differences in average RNFL thickness [58]. In another study on Swedish children, RNFL superior was thicker in left eyes, but average RNFL showed no differences [59]. A third study reported thicker RNFL thickness in all parameters of left eyes, but the average RNFL was not significantly different [60]. According to Pawar and Maheshwari [58], most of the studies using OCT suggest that the average degree of interocular symmetry is well preserved. So, the presence of asymmetry between the two eyes may further confirm an abnormality affecting the retinal nerve and hence the brain. However, in our study, we could not find sufficient evidence of this difference.

Explanation of possible difference between right and left eyes as regard OCT parameters is not yet well established; however, some possible explanations are suggested.

Angles between the maxima of peripheral RNFL thickness were higher in right than left eyes, and that RNFL asymmetry could be influenced by the locations of the supertemporal retinal artery and vein. The retinal vascular system also exhibits interocular asymmetry. It

was also reported that the mean central retinal arteriolar equivalent of right eyes was 3.14 μm larger than that of left eyes [61].

Asymmetry in neuronal connectivity that leads to ocular dominance that is a poorly understood concept. Ocular dominance is not associated with interocular macula thickness asymmetry but possibly associated with GCC and RNFL thickness [62].

Limitations of this study may include the relatively small size and the study's cross-sectional nature. Another limitation is the absence of a quantitative measure of serum tramadol level. Researchers who assessed both groups were not blind to the subjects' data. We could not exclude lifetime use of any substance as almost all patients used multiple substances during their substance history. However, we excluded patients fulfilling substance use disorder criteria according to DSM-5 for other substances rather than tramadol. Another limitation is that OCT is not a diagnostic procedure; it is more valuable to use it to follow up on the RNFL thickness along the disease course. Differences between right and left eyes were detected in GCC only and in both patients and controls, which decreases its significance. However, it may raise a possibility that some OCT changes could happen by chance, so larger sample studies may be needed to confirm the reported findings.

We recommend that further studies include more tramadol use patients and more advanced techniques like OCT angiography to examine the vascular effect of tramadol on the retina.

Conclusions

Long-term tramadol use is associated with decreased thickness of RNFL that can be a potential marker and early sign for degeneration detected by noninvasive techniques like OCT.

Screening for these changes should be a part of assessing patients with tramadol use; OCT can be a simple, noninvasive tool that achieves this purpose.

Abbreviations

ASI	Addiction Severity Index
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
GCC	Ganglion Cell Complex
MRI	Magnetic Resonance Imaging
OCT	Optical Coherence Tomography
REC	Research Ethics Committee
RNFL	Retinal Nerve Fiber Layer
SNRI	Serotonin-Norepinephrine Reuptake Inhibitors
SPSS	Statistical Package for the Social Sciences
SSRIs	Selective Serotonin Reuptake Inhibitors

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Authors' contributions

M. A. K. shared the study design, statistical analysis, manuscript preparation, and revision and read and approved the final manuscript. N. M. K. shared the ophthalmological assessment, manuscript preparation, and revision and read and approved the final manuscript. A. F. E. shared in the ophthalmological assessment, manuscript preparation and revision and read and approved the final manuscript. S. M. E. shared in psychiatric assessment, manuscript preparation, and revision and read and approved the final manuscript. A. A. S. shared in psychiatric assessment, manuscript preparation, and revision and read and approved the final manuscript. D. R. A. shared in psychiatric assessment, manuscript preparation, and revision and read and approved the final manuscript. All authors read and approved the final manuscript.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

The study protocol was approved by ethical committee of Kasr Al Ainy Faculty of Medicine (N-16–2018) and conducted following the tenets of the Declaration of Helsinki. Patients and control subjects signed informed written consents before participation in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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