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Evaluation of Lamina Cribrosa Changes in Patients with Primary Open- Angle Glaucoma by Swept Source Optical Coherence Tomography

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Abstract:

AIM: This study aimed to assess the lamina cribrosa changes in primary open angle glaucoma patient using Swept-source OCT and correlate the results with their perimetric changes.

METHODS:

This was a prospective observational cross- sectional and analytical study which held on 60 eyes with primary open angle glaucoma and 20 healthy control subjects. Measurement of intraocular pressure using Goldmann applanation tonometry and visual field assessment using standard automated perimetry (Humphrey Visual Field Analyser II; Carl Zeiss Meditec, Dublin, California, USA) were done. All subjects were scanned using Swept Source OCT device (Triton, Topcon, Tokyo, Japan) to measure RNFL thickness, mean lamina cribrosa depth and mean lamina cribrosa thickness. Independent sample T and Mann Whitney tests were used for analysis.

Results:

Mean age of control group was 59.15±6.78 years and of glaucoma group was 60.32±9.67 years, while mean IOP was 14.22±2.24mmhg, 17.34±7.56 mmhg in control group and POAG group, respectively. Rim area and rim volume were statistically significant with all grades of POAG (< 0.001), while RNFL thickness was statistically significant with moderate and severe groups only. The mean LC depth measured in the control group was 425.90±106.34 µm while measured 475.05±67.18 µm, 523.94±86.12 µm and 695.16±109.88 µm in the mild, moderate and severe groups respectively. The mean LC thickness was 156.68±22.23 µm while measured 141.79±32.64 µm, 126.16±21.45 µm, 115.76±16.68 µm in the mild, moderate and severe glaucoma groups respectively. However, they were no statistical significance with neither age nor CCT measurements of the patients.

Conclusion:

Lamina cribrosa depth and thickness by Swept-source OCT were statistically correlated with the grade of POAG severity.

Keywords: POAG, Swept source OCT, RNFL, Lamina cribrosa depth, Lamina cribrosa thickness.

Introduction:

Primary open-angle glaucoma (POAG) is described distinctly as a multifactorial optic neuropathy that is chronic, progressive, and irreversible, with a characteristic acquired loss of optic nerve fibers. Such loss develops in the presence of open anterior chamber angles, characteristic visual field abnormalities, and intraocular pressure that is too high for the continued health of the eye. It manifests by cupping of the optic disc in the absence of other known causes of the disease (1).

The Lamina Cribrosa (LC), which is located at the bottom of the optic disc cup, is composed of a series of sieve-like collagenous plates in the optic nerve head (ONH).

It is generally believed that a crucial part of the underlying pathogenesis of glaucoma is axonal constriction, which is followed by disturbances in axoplasmic flow and axonal damage in the LC(2).

Recently, optical coherence tomography (OCT) has been used for in vivo imaging of the LC(3). Advances in OCT technology, including deeper signal penetration and increased scanning speeds, allow in vivo 3-dimensional (3D) imaging of LC at an unprecedented beams and pores(4).

Swept-source (SS)-OCT, also known as high penetration (HP)-OCT, has been developed to enhance visualization of posterior ocular layers, including the LC (5).

The present study aimed to evaluate the lamina cribrosa changes in primary open angle glaucoma patient using Swept-source optical coherence tomography and correlate the results with their visual field changes.

PATIENTS AND METHODS

This was a prospective observational cross sectional and analytical study which held on 60 eyes with primary open angle glaucoma and 20 healthy control subjects attending to Mansoura ophthalmic center- Mansoura University, Egypt. Study protocol was submitted for approval by Mansoura medical research ethics committee, faculty of medicine, Mansoura University (code number: MS/17.04.106). Informed consent was obtained for each patient in the study after assuring confidentiality.

Inclusion criteria included patients with primary open-angle glaucoma with the following criteria; age above 40 years, visual acuity above 6/60, refractive error within ± 6.0 diopters equivalent sphere and within ± 3.0 diopters astigmatism , or less than 2.0 diopter anisometropia, open anterior chamber angle on gonioscopy, evidence of glaucomatous optic nerve head damage (e.g., neuroretinal rim thinning , notching, excavation , or retinal nerve fiber layer defect), glaucomatous pattern of visual field defect.

Exclusion criteria included patients with previous intraocular surgery or laser therapy, evidence of vitreoretinal disease or diabetic retinopathy, media opacity that does not permit optical coherence tomography acquisition with good signal strength, angle closure glaucoma or secondary glaucoma, evidence of neurological disorders that cause visual field defect mimicking glaucomatous changes, contraindications of pupil dilataion , eyes with unreliable visual field or poor quality imaging.

Ophthalmologic examination included: Visual acuity assessment using Snellen chart then converted to log MAR, anterior segment slit lamp examination (Haag Streit BP 900, Haag-Streit, Koeniz, Switzerland), refractive error and corneal curvature were measured using an autorefractor (Canon RK 5 Auto Ref-Keratometer; Canon Inc., Ltd., Tochigiken, Japan), central corneal thickness measurement using anterior segment OCT, fundus examination using a Volk lens 90 diopter, average of the axial length measurements by NIDEK AL-SCAN optical biometer, measurement of intraocular pressure using Goldmann applanation tonometer, assessment of anterior chamber angel using gonioscopy (three Goldmann goniolens), visual field assessment using standard automated perimetry (Swedish Interactive Threshold Algorithm Standard algorithm with a 24-2 test pattern, Humphrey Visual Field Analyser II; Carl Zeiss Meditec, Dublin, California, USA).

Swept-source optical coherence tomography (3D DRI OCT Triton [plus], Topcon Corporation, Tokyo, Japan) was performed using a high speed of 100,000 axial scans/second and center wavelength of 1,050 nm (version 10.07), digital and optical axial resolution of 2.6 μm and 8 μm in tissue, respectively and transverse resolution of 20 μm. Technique of OCT scanning was done as follows: Mydriatic (tropicamide 1%) eye drops were used achieve pupil dilatation. The chair height, chin rest and imaging machine were adjusted to approximate position, then patient was asked to fixate on a target point inside the instrument. Optic disc map for peripapillary RNFL thickness: three dimensional raster scan protocol covered an area of 6.0× 6.0 mm centered on the optic disc with 512 A-scans × 256 B-scans [3D (6.0×6.0 mm-512×256)], then SS-OCT scans were obtained using 6-mm, 12-radial line scans centered on the optic disc.

Bruch's Membrane Opening distance (BMO) is manually determined by measuring the distance between the Bruch's membrane end-points of the optic nerve head,

which was shown by the red line. The line connecting Bruch's membrane edges was used as a reference plane for all depth measurements. The distance between the reference line defining the BMO and the anterior reflectivity of the LC (Blue dashed line) was measured perpendicular to the BMO line. The thickness of the LC was defined as the distance between the anterior and posterior borders of the highly reflective region (yellow dashed line) in the horizontal cross-sections of the ONH. All the measurements were taken at the horizontal and the vertical scans and then the mean was taken.

Statistical analysis:

Statistical Package for the Social Sciences for windows version 20.0. (Armonk, NY: IBM Corp) was used for statistical analysis. Shapiro-Wilk test was used to check the normality of the data distribution. All tests were conducted with 95% confidence interval. Charts were generated using SPSS' chart builder and Microsoft Excel for windows (2019). Quantitative variables were expressed as mean and standard deviation while categorical variables were expressed as frequency and percentage. Independent sample T and Mann Whitney tests were used for inter-group comparison of parametric and non-parametric continuous data respectively. One-way ANOVA with Bonferroni post hoc analysis and Kruskal Wallis with Dunn's post hoc analysis tests were used for comparison of parametric and non-parametric continuous data respectively. Fisher exact and Chi square tests were used for inter-group comparison of nominal data using the crosstabs function. P value was considered statistically significant at the > 0.05.

RESULTS

The study included 80 eyes of 80 patients (20 eyes were control, and 60 eyes were POAG). Glaucoma group was further subdivided into mild, moderate and severe groups according to perimetric changes, each group included 20 eyes.

The mean age of the control group was 59.15 ± 6.78 years and of the glaucoma group was 60.32 ± 9.67years. 45% were male and 55% were females in the control group while 58% were males and 48% were females in the glaucoma group as shown in table (1).

Table 1: Demographic data for control and POAG groups

		Control group (n= 20)	POAG group (n= 60)	95% CI	p
Age		59.15 ± 6.78	60.32 ± 9.67	- 5.12, 2.78	0.56
Gender	**Male**	45% (9)	58% (35)	-0.12, 0.39	0.44
	Female	55% (11)	42% (25)		
Side	**Right**	60% (12)	45% (27)	-0.4, 0.1	0.31
	Left	40% (8)	55% (33)		

Data is expressed as mean and standard deviation or as frequency and percentage. 95% CI: 95% confidence interval of mean difference between both groups. P is significant when < 0.05.

Mean BCVA in control group is 0.810± 0.180, and in POAG subgroups (mild, moderate, severe) were 0.644 ± 0.112, 0.526 ± 0.149 and 0.449 ± 0.136, respectively, (< 0.001) . Regarding mean IOP, it was 14.22 ± 2.24 mmhg in control group, 16.39 ± 1.18 mmhg in mild glaucoma group, 16.88 ± 2.13 in moderate group, 19.17 ± 0.93 mmhg in severe glaucoma group (< 0.001). About the mean axial length, it was measured as 23.79 ± 0.62 mm in control group, 24.37 ± 0.70 mm in mild glaucoma group, 24.42 ± 0.67 mm in moderate group and 24.82 ± 0.72 mm in severe glaucoma group(< 0.001)

Table (2): Comparison of BCVA, IOP and axial length between control and grades of glaucoma:

	Control group (n= 20)	Mild POAG (n= 20)	Moderate POAG (n= 20)	Severe POAG (n= 20)	P
BCVA	0.810 ± 0.180	0.644 ± 0.112	0.526 ± 0.149	0.449 ± 0.136	< 0.001*
IOP	14.22 ± 2.24	16.39 ± 1.18	16.88 ± 2.13	19.17 ± 0.93	< 0.001*
Axial length	23.79 ± 0.62	24.37 ± 0.70	24.42 ± 0.67	24.82 ± 0.72	< 0.001*

Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of mean difference between both groups. *: P is significant when < 0.05.
BCVA: Best corrected visual acuity; IOP: Intraocular pressure

Mean VCDR in control group is 0.46± 0.10, and in POAG subgroups (mild, moderate, severe) were 0.60 ± 0.093, 0.70 ± 0.088 and 0.83 ± 0.093, respectively, (< 0.001) . Regarding mean rim area , it was 1.64 ± 0.22 in control group, 1.35 ± 0.183 in mild glaucoma group, 1.05 ± 0.153 in moderate group, 0.90 ± 0.304i n severe glaucoma group (< 0.001). About the mean rim volume, it was measured as 0.45 ± 0.14 in control group, 0.62 ± 0.091 in mild glaucoma group, 0.20 ± 0.068i n moderate group and 0.18 ± 0.087 in severe glaucoma group (< 0.001).There was statistically significant differences observed between control and glaucoma subgroups (< 0.001). No statistically significant difference observed between control and glaucoma subgroups regarding disc

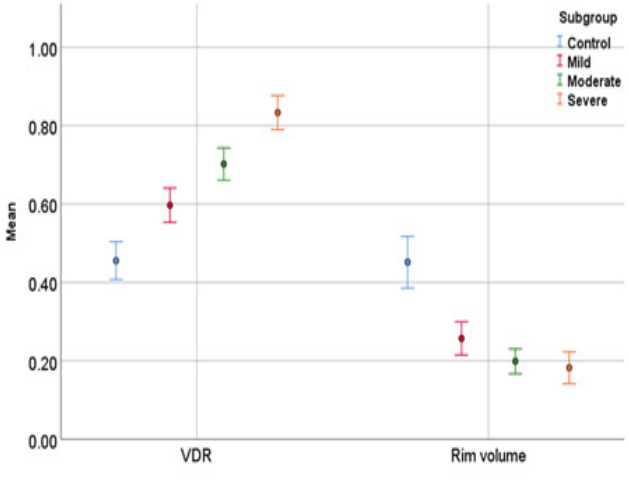
area (0.49) (Table 3) (Fig. 1).

Table (3): Comparison of optic disc,rim area, rim volume, and RNFL measurements between control and POAG grades

	Control group (n= 20)	Mild POAG (n= 20)	Moderate POAG (n= 20)	Severe POAG (n= 20)	P
Disc area	2.29 ± 0.36	2.23 ± 0.276	2.19 ± 0.287	2.15 ± 0.272	0.49
VCDR	0.46 ± 0.10	0.60 ± 0.093	0.70 ± 0.088	0.83 ± 0.093	< 0.001*
Rim area	1.64 ± 0.22	1.35 ± 0.183	1.05 ± 0.153	0.90 ± 0.304	< 0.001*
Rim volume	0.45 ± 0.14	0.26 ± 0.091	0.20 ± 0.068	0.18 ± 0.087	< 0.001*
RNFL thickness	98.33 ± 7.62	89.48 ± 10.362	72.23 ± 12.700	61.80 ± 11.593	< 0.001*

Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of mean difference between both groups. *: P is significant when < 0.05.
VCDR: Vertical cup disc ratio, RNFL: Retinal nerve fiber layer.

Figure (1): VDR and rim volume in the studied groups



The mean LC depth measured in control group was 425.90 ± 106.34 µm, and 475.05 ± 67.18 µm, 523.94 ± 86.12 µm and 695.16 ± 109.88 µm in mild, moderate and severe POAG groups, respectively, (< 0.001) (Figure 2). The mean LC thickness was 156.68 ± 22.23 µm while measured 141.79 ± 32.64 µm, 126.16 ± 21.45 µm, 115.76 ± 16.68 µm in the mild, moderate and severe POAG groups, respectively, (< 0.001) as shown in table (4).

Figure (2): Lamina cribrosa depth in the studied groups

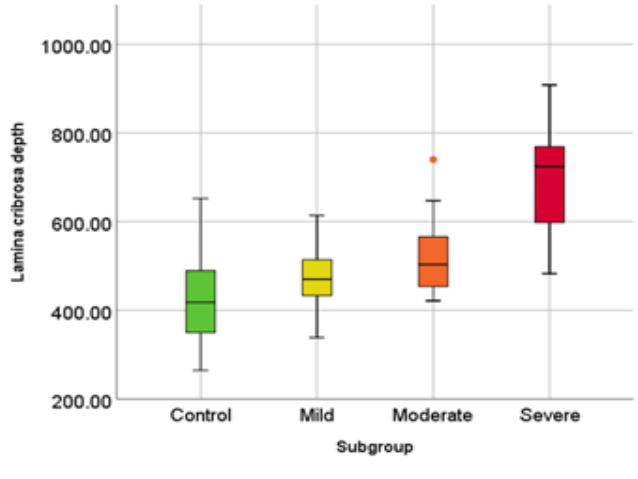


Table (4): Comparison of lamina cribrosa thickness and depth measurements between control and POAG grades.

	Control group (n= 20)	Mild POAG (n= 20)	Moderate POAG (n= 20)	Severe POAG (n= 20)	p
Lamina Cribrosa Depth	425.90 ± 106.34	475.05 ± 67.18	523.94 ± 86.12	695.16 ± 109.88	< 0.001*
Lamina Cribrosa Thickness	156.68 ± 22.23	141.79 ± 32.64	126.16 ± 21.45	115.76 ± 16.68	< 0.001*

Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of mean difference between both groups.*: P is significant when < 0.05.

Mean LC depth measurements were statistically significant with the IOP, axial length, RNFL thickness and MD f the patients, while LC depth was not statistically significant with the age nor the CCT of the patients (Table 5).

Table (5); Correlation between lamina cribrosa depth and age, IOP, axial length, RNFL thickness, CCT and MD.

Variables	Correlation coefficient	95% CI	P
Age	0.005	-0.215, 0.225	0.962
IOP	0.532	0.353, 0.673	< 0.001*
Axial length	0.298	0.084, 0.486	0.007*
RNFL Thickness	-0.498	-0.647, -0.313	< 0.001*
CCT	-0.122	-0.333, 0.101	0.281
MD	-0.544	-0.682, -0.368	< 0.001*

95% CI: 95% confidence interval of correlation coefficient. *: P is significant when < 0.05.
IOP: intra-ocular pressure, RNFL: retinal nerve fiber layer, CCT: central corneal thickness, MD: mean deviation

In addition, mean LC thickness measurements were statistically significant with IOP, axial length, RNFL thickness and MD measurements of the patients. However, they were not statistically significant with neither the age nor CCT measurements of the patients as shown in table (6).

Table (6): Correlation between lamina cribrosa thickness and age, IOP, axial length, RNFL thickness, CCT and MD.

Variables	Correlation coefficient	95% CI	P
Age	-0.179	-0.384, 0.042	0.112
IOP	-0.458	-0.616, -0.265	< 0.001*
Axial length	-0.278	-0.469, -0.062	0.012*
RNFL Thickness	0.456	0.263, 0.614	< 0.001*
CCT	0.064	-0.158, 0.279	0.575
MD	0.484	0.296, 0.636	< 0.001*

95% CI: 95% confidence interval of correlation coefficient. *: P is significant when < 0.05.
IOP: intra-ocular pressure, RNFL: retinal nerve fiber layer, CCT: central corneal thickness, MD: mean deviation

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DISCUSSION

Primary open-angle glaucoma (POAG) is a chronic progressive optic neuropathy. The resultant loss of retinal ganglion cells (RGCs) and their axons leads to a characteristic acquired optic atrophy (6). The lamina cribrosa is a mesh-like structure that surrounds and protects the RGC axons at the optic nerve head (7). Deformation and displacement of the lamina cribrosa can block the axoplasmic flow within RGC axons (8). Thus, the lamina cribrosa is a key site for axonal injury in glaucomatous optic neuropathy (9).

Optical Coherence tomography has become an important imaging method in ophthalmology where it is mainly used for diagnosis and follow-up of glaucoma and retinal diseases (10). Swept-source optical coherence tomography (SS-OCT) is a novel imaging technology, with higher scanning speed, longer wavelength, and improved signal detection than SD-OCT, achieving better simultaneous imaging of both superficial and deep tissue structures (11). These features improve visualization and quantification of localized and subtle glaucomatous changes of the ONH(12).

Lamina cribrosa depth is often defined as the maximal or average vertical distance from the anterior LC surface to the reference plane of Bruch membrane opening (13), (14). In the present study, the mean LC depth measured in the control group was 425.90 ± 106.34 μm, and 475.05 ± 67.18 μm, 523.94 ± 86.12 μm and 695.16 ± 109.88 μm in the mild, moderate and severe groups respectively. The mean LC depth was of no statistical significance with the mild glaucoma group, while was statically significant with the moderate and the severe glaucoma groups. These results were similar to Kazuko et al., (15). In contrast, Park et al., (16) revealed that LC posterior displacement has been found to occur mostly in the initial stages of glaucoma.In that study, the LC depth was greatest in mild-to-moderate POAG.

cross-sectional studies have investigated the factors associated with LC depth. Regarding age, which is a crucial factor relevant to LC depth, in the present study study. there was no statistical significance between LC depth and age (P =0.962). This was similar to You Na et al., (17) where (P =0.630). Also there was no statistically significant between LC depth and age in Haomin Luo et al., (18); Yong et al., (19). This negative correlation of LC depth with age in cross-sectional studies may be because the ONH and peripapillary scleral connective tissues stiffen with age (20),(21).

Regarding the axial length, the present study showed statistically significant between LC depth and the axial length (P value =0.007). This was similar to Sung-Cheol et al., (22) where (P = 0.022). However, studies concluded that there was no statistically correlation between LC depth and the axial length (17),(18) (19).

For IOP, our study illustrated statistical significance between LC depth and IOP (P value < 0.001), and this was similar to what was found in You Na et al., (17); Haomin Luo et al., (18); Yong et al., (19). It was found that for each millimeter of mercury increase in the average IOP during follow up, the LC surface was displaced posteriorly by 2.0 mm displacemen (23)t. In contrast, another prospective study observed only decreased prelaminar thickness with no LC depth change for elevated IOP (mean change: 12.4mmHg, duration: <2 minutes), both in healthy subjects and glaucoma patients (24).

As regards to RNFL thickness, there was statistical significance between LC depth and RNFL thickness (P value < 0.001) as in Jeong-Ah et al., (25). Moreover, experimental studies have shown that posterior displacement of the LC precedes early surface-detected structural damage and RNFL loss (26) . Based on these considerations, it has been proposed that evaluation of LC morphology is useful in predicting progression to manifest glaucoma among patients with suspected glaucoma (25). In addition, CCT had no statistical significance with LC depth in our study (P value = 0.281). This was similar to results found in Yong et al., (19).

The present study revealed statistical significance between MD and LC depth (P value < 0.001). This was similar to Haomin Luo et al., (18), Kyoung et al., (27). In contrast to Yong et al., (19), which stated that there was no significant correlation between LC depth and VF mean deviation (MD), and explained that this is consistent with other findings, which determined that ONH surface depression occurred before RNFL thinning in a considerable proportion of glaucoma patients (23).

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OCT-measured LC thickness, defined as the distance between the anterior and posterior borders of the LC, has attracted clinicians seeking the pathogenesis of glaucoma (19). In the present study, the mean LC thickness was 156.68 ± 22.23 µm while measured 141.79 ± 32.64 µm , 126.16 ± 21.45 µm and 115.76 ± 16.68 µm in the mild, moderate and severe glaucoma groups respectively. These results were lower that found in Kazuko et al., (15), where mean LC thickness was 268 ± 23 µm in the control group and 248 ± 13 µm in the glaucoma group. In the present study, LC thickness was statistically significant with grades of glaucoma (P value < 0.001). That was similar to results found in Kazuko et al., (15), where (P < 0.01).

By investigating possible influencing factors on LC thickness, as regard to age for example, our study showed no statistical significance between LC thickness and age (p value = 0.112). This was similar to Kazuko et al., (15) . However, there was significant correlation between LC thickness and age in Kyoung et al., (27) . It speculated that it could be associated with age-related changes in the connective tissue; Maintaining a high rate of matrix remodeling with matrix metalloproteinase is an important mechanism for conserving the plasticity of the lamina cribrosa in physiologic conditions (28). Since aging generally involves increased sequestration of matrix metalloproteinase (MMP) and a reduced turnover of the extracellular matrix (29), it can be supposed that older eyes would have a thicker and stiffer lamina cribrosa. Human ex-vivo studies have found that advancing age is associated with a thicker lamina cribrosa (30) and changes in the composition of the extracellular matrix (31).

Regarding the axial length, it was statistically significant with LC thickness in the present study (P value = 0.012). However, there was no significant correlation between axial length and LC thickness in Kazuko et al., (15); Yong et al., (19). In the present study, there was no significant correlation between CCT and LC thickness (P value = 0.575), which matched the results in Kazuko et al., (15); Yong et al., (19).

Regarding IOP and RNFL thickness, they were statistically significant with LC thickness in our study (P value < 0.001). This was similar to Yong et al., (19), Inoue et al., (32). In contrast to Kazuko et al., (15) which revealed that IOP was not significantly affecting LC thickness (P value = 0.446). Regarding MD, we found that it was statistically significant with LC thickness (P value < 0.001). This was similar to results found in Kazuko et al., (15) where (P value = 0.013), so they found that LC thickness was an excellent structural biomarker for glaucoma diagnosis, and that it promises to help future investigations into the pathophysiology of glaucoma.

CONCLUSION

Lamina cribrosa depth and thickness are not only correlated to the grade of glaucoma severity; but also other risk factors including age, axial length, IOP, RNFL thickness and MD. Swept-source optical coherence tomography (SS-OCT) achieving better simultaneous imaging of both superficial and deep tissue structures. These features improve visualization and quantification of localized and subtle glaucomatous changes of the ONH.

DECLARATIONS:

Ethics approval and consent to participation; This observational cross section study was approved by the ethics committee of Faculty of medicine, Mansoura university (Registration Number : MS/17.04.106 , Date: 29-4-2017) and adhered to the tents of Declaration of Helsinki. All subjects provided written informed consent prior to study participation.

Consent for publication; Not applicable

Availability of data and materials; Data are available upon request

Competing of interests; The authors declare that they have no conflict of interest

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Authors contributions; Abd-Elrahman M H, and Ghanem A A designed the study, Gaafar WM.,and Elsebaey S S performed examinations of individulas, Elsebaey S S prepared and carried out the analysis, interpreted and discussed the results, and wrote the first version of the manuscript. All authors read and approved the final manuscript.

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