

RESEARCH ARTICLE

Evaluation of optic nerve subarachnoid space in primary open angle glaucoma using ultrasound examination

Gilda Cennamo^{1*}, Daniela Montorio², Maria Angelica Breve², Vincenzo Brescia Morra², Feliciano Menna², Giovanni Cennamo²

1 Department of Public Health, University of Naples Federico II, Naples, Italy, **2** Department of Neurosciences, Reproductive Sciences and Dentistry, University of Naples Federico II, Naples, Italy

* xgilda@hotmail.com



Abstract

Objectives

To measure Optic Nerve Subarachnoid Space (ONSAS) in patients with primary open-angle glaucoma (POAG) and controls using A-scan ultrasound and to evaluate the measurement of the ONSAS in relation to age patient and OCT parameters.

Methods

This retrospective study included 53 consecutive eyes of 27 patients with POAG and 64 normal eyes of 32 controls. Both glaucomatous and control groups were divided into 2 subgroups according to age: <60 age (glaucomatous and control group 1) and 61–90 age (glaucomatous and control group 2).

Results

The ONSAS was significantly lower in all glaucomatous eyes (3.54 ± 0.38) versus normal eyes (3.87 ± 0.32) ($p = 0.001$). Significant reduction of ONSAS was showed in control group 2 ($3.63 \text{ mm} \pm 0.37$) compared to control group 1 ($3.87 \text{ mm} \pm 0.32$) ($p = 0.014$) and between glaucoma group 1 ($3.54 \text{ mm} \pm 0.38$) and control group 1 ($p = 0.001$). While no significant differences were observed between glaucomatous group 2 ($3.48 \text{ mm} \pm 0.41$) and control group 2 ($p = 0.17$) and between glaucoma group 1 and glaucoma group 2 ($p = 0.609$). Lastly, the ONSAS was not significantly associated with GCC and RNFL parameters except for Focal Loss Volume (FLV), Superior RNFL and ONSAS in glaucoma group 1 and for FLV and ONSAS in all glaucomatous group.

Conclusion

Standardized A-scan ultrasound is a non invasive imaging technique with which it is possible to monitor ONSAS changes in glaucomatous patients. The reduction of ONSAS confirm the importance of the lower orbital CSFP as further risk factor in the progression of glaucoma disease.

OPEN ACCESS

Citation: Cennamo G, Montorio D, Breve MA, Brescia Morra V, Menna F, Cennamo G (2018) Evaluation of optic nerve subarachnoid space in primary open angle glaucoma using ultrasound examination. PLoS ONE 13(11): e0208064. <https://doi.org/10.1371/journal.pone.0208064>

Editor: Ahmed Awadein, Faculty of Medicine, Cairo University, EGYPT

Received: September 20, 2018

Accepted: November 9, 2018

Published: November 28, 2018

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Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Introduction

Primary open angle glaucoma (POAG) is the most common form of glaucoma characterized by a progressive cupping of the optic nerve head due to thinning of the neuroretinal rim, ganglion cell and retinal nerve fiber layers [1].

Increased intraocular pressure (IOP) has long been considered to be the major risk factor for the development and progression of glaucomatous damage [2].

Because many patients, though normal IOP measurements, showed optic nerve damages, additional factors have been hypothesized [3].

The study conducted by Volkov showed that cerebrospinal fluid pressure (CSFP) could pathogenically be correlated with glaucomatous optic neuropathy [4].

In-fact the lamina cribrosa is exposed not only to IOP in the eye but also to CSFP in optic nerve subarachnoid (ONSAS).

The lamina cribrosa separates these two pressurized regions. The pressure drop that occurs across the lamina cribrosa, (IOP-ICP), is known as translaminar pressure difference and is typically directed posteriorly [5].

Different studies have suggested that both elevated IOP and reduced CSFP increase translaminar pressure and play an important role in the pathogenesis and progression of glaucoma disease [6–9].

In previous studies the translaminar pressure difference was evaluated on lumbar CSFP measurement, an invasive technique that reflects the CSFP in ONSAS [10].

This direct measurement of the CSFP is an invasive method and not always acceptable in clinical practice, then it is preferred to use a non-invasive technique to estimate the CSFP in ONSAS.

The purpose of this retrospective study was to measure the ONSAS, using A-scan ultrasound, in POAG and control eyes and to evaluate the ONSAS in relation to age patient and OCT parameters.

Materials and methods

In this retrospective study we evaluated 53 consecutive eyes of Caucasian 27 patients (16 females, 11 males, mean age 69.8 ± 13.3 years) presenting open-angle glaucoma enrolled from March to June 2016 in the Eye Clinic of the University of Naples “Federico II”. Each patient underwent evaluation of best corrected visual acuity (BCVA) according to the Early Treatment of Diabetic Retinopathy Study (ETDRS), Goldman applanation tonometry, gonioscopy, slit-lamp biomicroscopy, fundus examination with a +90 D lens, standard visual field perimetry (Humphrey Field analyzer with Swedish Interactive Thresholding Algorithm SITA standard 30–2 test program (Carl Zeiss Meditec Dublin, CA, USA), RTVue-100 FD-OCT, software version A5, 1, 0, 90 (Optovue, Inc., Fremont, CA, USA) and standardized A-Scan Ultrasound (Aviso S System, Quantel Medical, Bozeman, MT).

Glaucomatous eyes were defined as those with a glaucomatous visual field defect, optic nerve head changes and open angle on gonioscopy. All patients, under topical medication, showed values of IOP within the normal range at the time of ultrasound examination. They were divided according to age: <60 age (glaucomatous group 1: 27 eyes), 61–90 age (glaucomatous group 2: 26 eyes).

The control group was constituted by 32 individuals (18 females, 14 males; for a total of 64 eyes) that had an unremarkable ophthalmic examination, intraocular pressure below 21mmHg, normal visual field tests and OCT examination and no history of glaucoma in a first-degree relative. Also controls were divided according to age: <60 age (control group 1: 32 eyes), 61–90 age (control group 2: 32 eye).

Exclusion criteria for all participants were: current or past ocular pathology that could cause VF changes or optic disc abnormalities; history of intraocular surgery, clinically relevant opacities of the optic media that could influence quality images of OCT; neurological disorder or use of drugs that could influence intracranial pressure; current or past lumbar punctures, cranial surgery and brain trauma.

The study was approved by the Institutional Review Board of the University of Naples “Federico II” and all investigations adhered to the tenets of the Declaration of Helsinki. Written informed consents were obtained from the patients enrolled in the study.

A-Scan ultrasound

The measurement of the ONSAS was determined by echographic examination using the standardized A-scan method as described by Ossoinig and associates [11–13]. Topical anesthetic was instilled in the conjunctival sac of all participants before starting the exam. After application of gel on the probe, the A-scan probe was placed on the eye in the primary position at lateral canthus and was angled back at the orbital level of the optic nerve until the characteristic optic nerve pattern was obtained on the echographic screen. All measurements were performed at a distance of approximately 2 to 5 mm posterior to the globe. When the sound beam was perpendicular to the surface of the anterior third of the optic nerve, the highest double spikes that corresponded to arachnoid surfaces were obtained from each side of the nerve.

By placing electronic gates over the peaks of the two maximized arachnoid spikes, the maximum arachnoid space diameter was measured (arrows in Fig 1). Moreover longitudinal and transverse B-scans of the optic nerve were performed to confirm that the sound beam of A-scan probe is perpendicular to the surface of the anterior third of the optic nerve (Fig 2). All

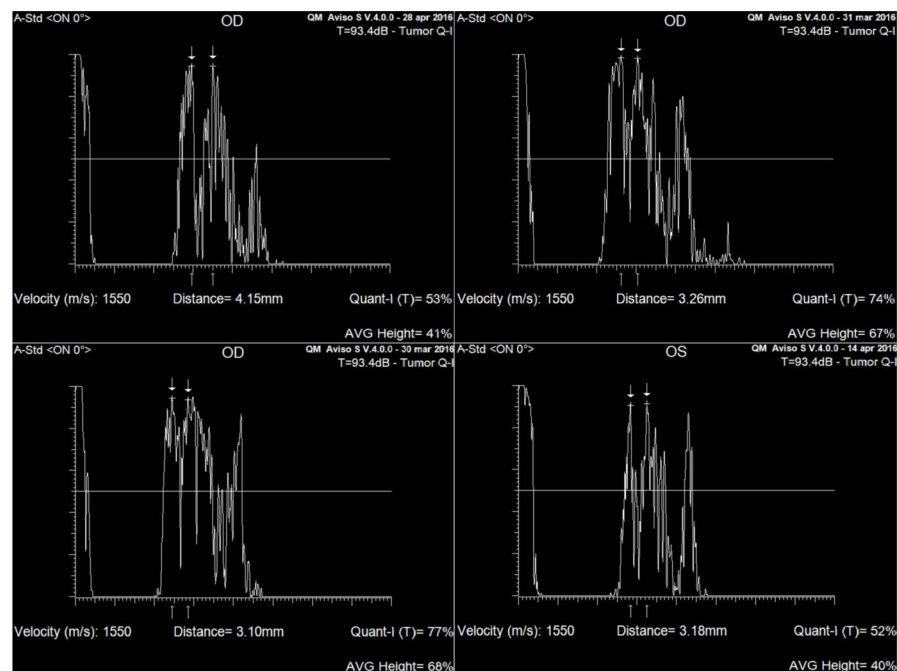


Fig 1. Echograms showing optic nerve subarachnoid space (ONSAS) measurements, using the standardized A-scan ultrasound in control group 1 and 2 in top row (left and right panel, respectively) and in glaucomatous group 1 and 2 in bottom row (left and right panel, respectively). The arrows over the peaks of the two high and perpendicular spikes, as shown in echograms, indicate the maximum arachnoid space diameter measured in the anterior third of the optic nerve.

<https://doi.org/10.1371/journal.pone.0208064.g001>

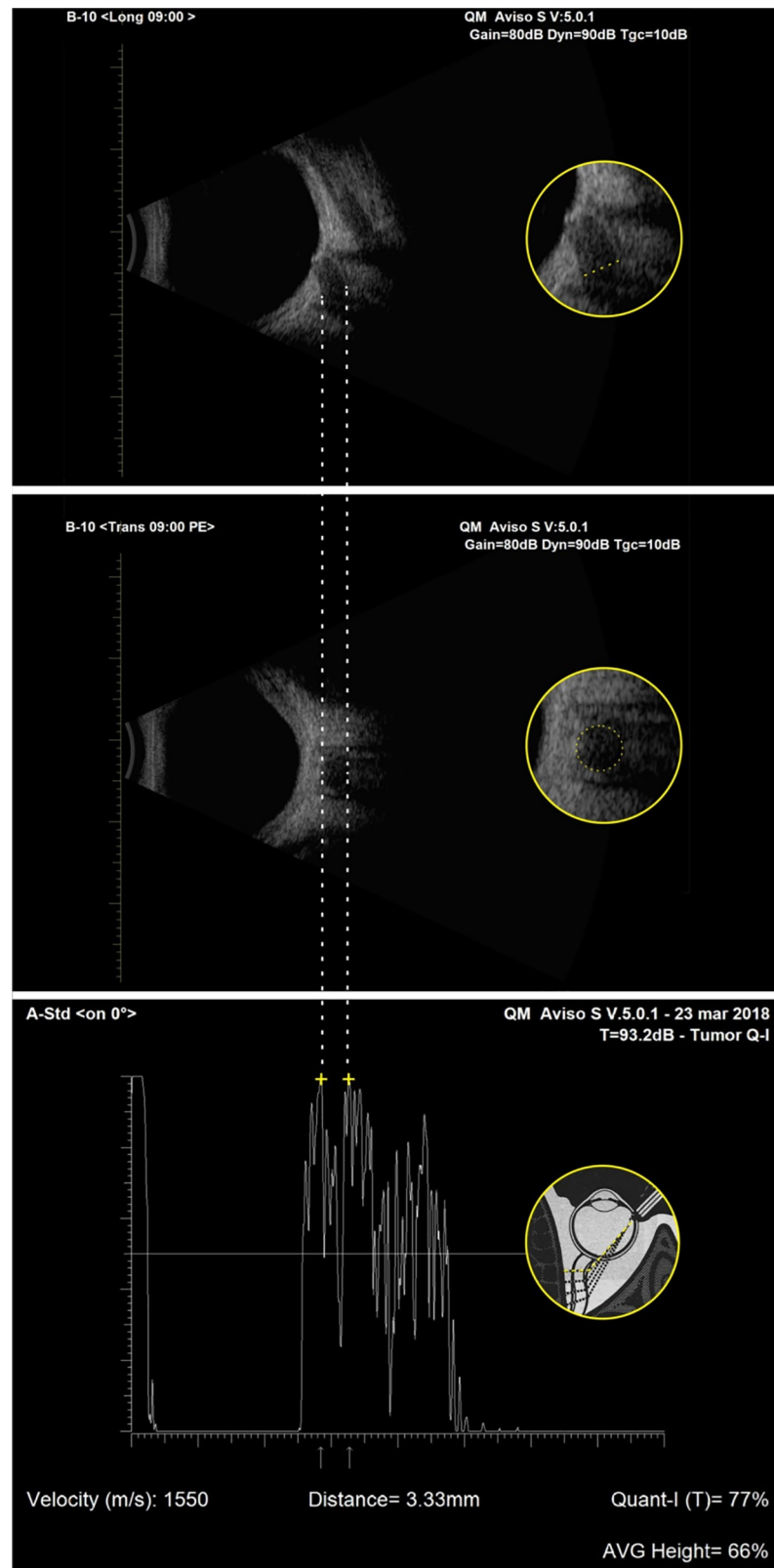


Fig 2. Longitudinal (top) and transverse (middle) B-scan echograms of the optic nerve confirm that the sound beam of A-scan probe is perpendicular to the surface of the anterior third of the optic nerve (yellow dashed line) (bottom).

<https://doi.org/10.1371/journal.pone.0208064.g002>

measurements were performed by the same experienced examiner not informed with glaucoma diagnosis.

Spectral domain optical coherence tomography

The retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thickness were evaluated, after pupillary dilation (minimum diameter 5 mm), with SD-OCT (RTVue-100 OCT, Optovue Inc., Fremont, CA, USA; software version A5, 1, 0, 90) which captures 26,000 axial scans (A-scans) per second and provides a 5- μ m depth resolution in tissue. The optic nerve head map protocol was used to evaluate the cpRNFL. This protocol generates a cpRNFL thickness map based on measurements obtained around a circle 3.45 mm in diameter centered on the optic disc. The GCC scan was centered 1-mm temporal to the fovea and covered a square grid (7 \times 7 mm) on the central macula, and GCC thickness was measured from the internal limiting membrane to the outer boundary of the inner plexiform layer. Only high-quality images, as defined by a signal strength index above 35, were accepted. The examiner rejected scans that had motion artifacts, poor centration, incorrect segmentation or poor focus [14].

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (Version 20.0 for Windows; SPSS Inc, Chicago, Ill, USA). Student's t-test analysis for independent samples was used to compare ONSAS values between the glaucomatous and control groups and between patient groups divided according to age. Spearman's correlation was used to study the associations between ONSAS values and SD-OCT parameters in glaucomatous group. A p value of < 0.05 was considered statistically significant.

Results

In this retrospective study, 27 patients (16 females, 11 males, mean age 69.8 ± 13.3 years) for a total of 53 eyes were enrolled. Mean BCVA was 0.18 ± 0.2 log MAR and mean IOP was 16.7 ± 2.5 mmHg. The control group was constituted by 32 individuals (18 females, 14 males, mean age 67.7 ± 13.2 years) for a total of 64 eyes examined. There were neither significant age ($p = 0.412$) or IOP ($p = 0.112$) differences between patients and controls.

As shown in Table 1, the ONSAS was significantly lower in all glaucomatous eyes ($p = 3.54 \pm 0.38$) versus normal eyes ($p = 3.87 \pm 0.32$) ($p = 0.001$).

Different results are showed comparing patients and controls divided according to age. ONSAS was significantly different ($p = 0.001$) between glaucoma group 1 ($3.54 \text{ mm} \pm 0.38$) and control group 1 ($3.87 \text{ mm} \pm 0.32$). While ONSAS did not differ ($p = 0.17$) between glaucomatous groups 2 ($3.48 \text{ mm} \pm 0.41$) and control group 2 ($3.63 \text{ mm} \pm 0.37$) (Fig 3). No significant differences were observed between glaucoma group 1 and glaucoma group 2 ($p = 0.609$). While significant reduction of the ONSAS was showed in control group 2 compared with control group 1 ($p = 0.014$) (Fig 4). Lastly, no significant correlation was found between OCT parameters and ONSAS of glaucomatous patients, except for Focal Loss Volume (FLV) ($P = 0.023$), Superior RNFL ($p = 0.044$) and ONSAS in glaucoma group 1 and for FLV ($p = 0.028$) and ONSAS in all glaucomatous group (Fig 5).

Discussion

To our knowledge, this is the first study to use standardized A-Scan ultrasound to evaluate the measurement of ONSAS in POAG patients.

Table 1. Demographic and clinical information of glaucomatous and control groups.

	POAG (mean ± SD)	Controls (mean ± SD)	p-value
Eyes, n	53	64	-
Gender (male/female), n	11/16	14/18	-
Age, years	69.8 ± 13.3	67.7 ± 13.2	0.412
IOP (mm hg)	16.7 ± 2.5	16 ± 2.4	0.112
CCT (µm)	552.3 ± 9.3	551.8 ± 8.9	0.769
ONSAS (mm)	3.54 ± 0.38	3.87 ± 0.32	0.001
GCC Average (µm)	91.33 ± 13.73	98.05 ± 4.39	0.001
GCC Superior (µm)	92.59 ± 18.44	99.29 ± 9.21	0.018
GCC Inferior (µm)	90.06 ± 11.44	98.13 ± 4.13	<0.001
FLV (%)	4.01 ± 7.32	1.29 ± 1.12	0.010
GLV (%)	8.46 ± 10.93	3.79 ± 1.82	0.003
RNFL Average (µm)	92.14 ± 15.33	102.68 ± 13.09	<0.001
RNFL Superior (µm)	94.23 ± 17.65	104.45 ± 13.84	0.001
RNFL Inferior (µm)	89.96 ± 15.18	100.97 ± 13.99	<0.001

POAG: Primary Open Angle Glaucoma; IOP: Intraocular Pressure, CCT: Central Corneal thickness

ONSAS: Optical Nerve Subarachnoid Space; GCC: Ganglion Cell Complex; RNFL: Retinal Nerve Fiber Layer.

Data are expressed as mean ± SD except for eyes and gender; Statistical significance P <0.05

<https://doi.org/10.1371/journal.pone.0208064.t001>

We found a statistically significant reduction in ONSAS in all glaucomatous eyes compared with normal eyes.

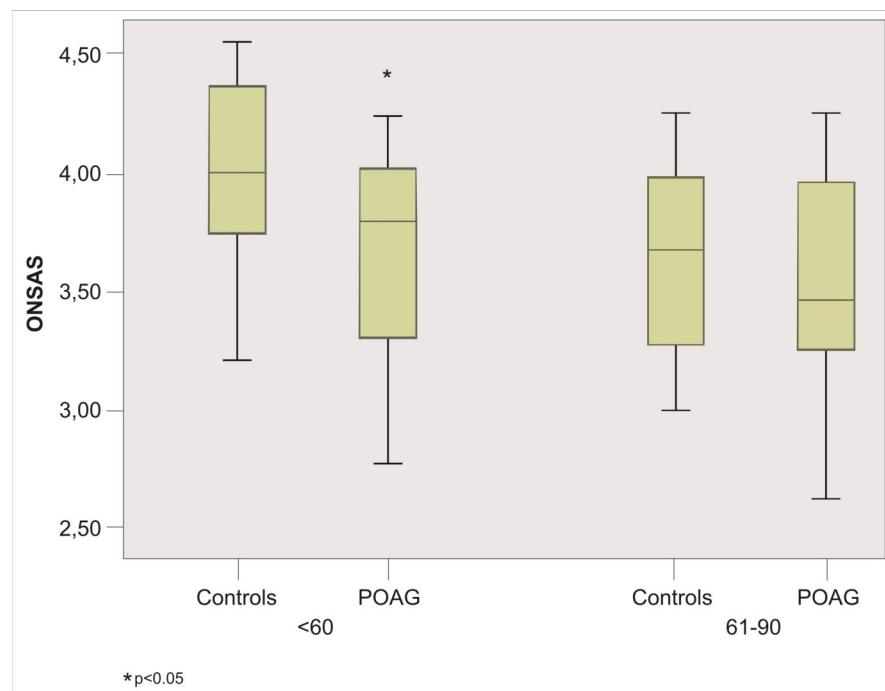


Fig 3. Box plots showing A-scan ultrasound measurements of the optic nerve subarachnoid space (ONSAS) in primary open angle glaucoma (POAG) and control groups that were compared according to age patient.

<https://doi.org/10.1371/journal.pone.0208064.g003>

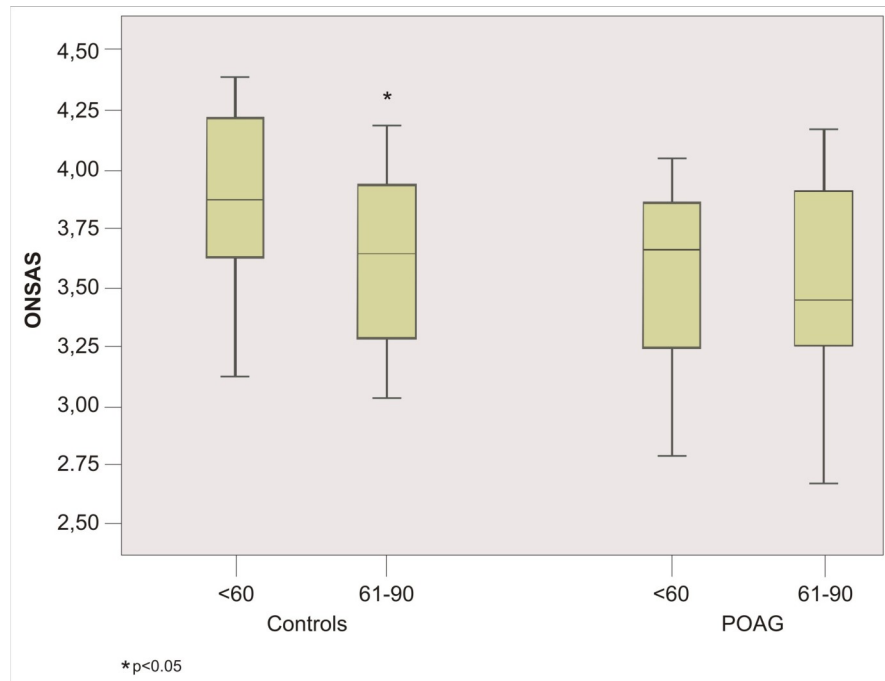


Fig 4. Box plots showing A-scan ultrasound measurements of the optic nerve subarachnoid space (ONSAS) that were compared between the younger (< 60 age) and older (61–90 age) subjects in each glaucomatous and control group.

<https://doi.org/10.1371/journal.pone.0208064.g004>

Our results are in line with the study conducted by Liu et al. that identified, using B-Scan ultrasound, a reduction of ONSAS in Normal Tension Glaucoma (NTG) and POAG patients respect to controls [15].

In our study we also evaluated the measurement of ONSAS in relation to age patient.

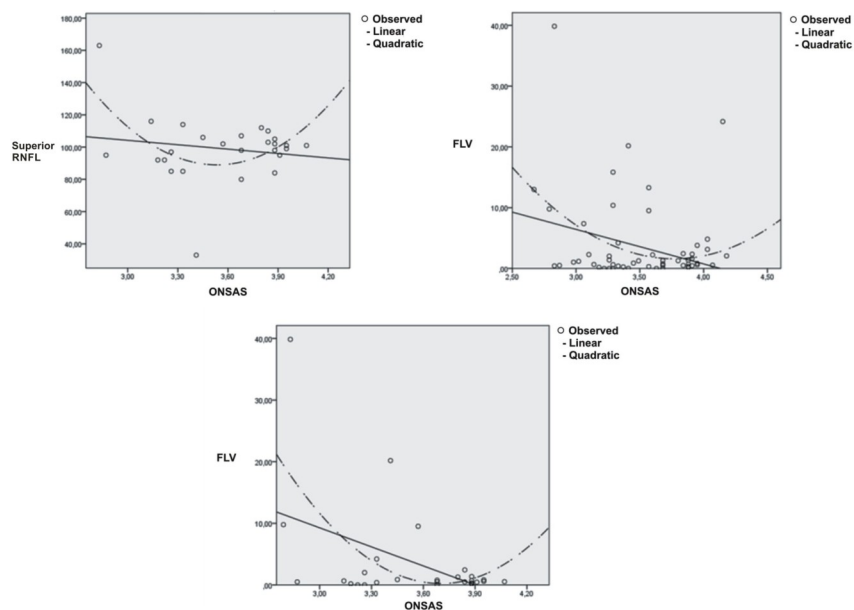


Fig 5. Scatter plots showing significant correlations between the optic nerve subarachnoid space (ONSAS) and superior retinal nerve fiber layer (Superior RNFL) (top left) and between ONSAS and focal loss volume (FLV) in glaucoma group 1 (top right) and between ONSAS and FLV in all glaucomatous group (bottom).

<https://doi.org/10.1371/journal.pone.0208064.g005>

We showed a statistically significant reduction in ONSAS in glaucoma group 1 (< 60 years) compared with control group 1 (< 60 years).

This finding is in line with the study, conducted by Berdhal et al, that showed significant differences in CSFP between POAG group and controls in < 60 age category of patients [7].

The glaucoma contributes to decline of CSFP determining a significant reduction of ONSAS although the progressive reduction of CSFP begins physiologically after age 60, as demonstrated by several studies [9,16].

The comparison between control group 1 (< 60 years) and control group 2 (> 60 years) was also statistically significant confirming different studies that have reported the steady decline of CSFP with a percent reduction from 2.5% for the 50–54 age group to 26.9% for the 90–95 age group in normal subjects [16].

In our study there was no significant differences in ONSAS comparing younger and older glaucomatous patients. The glaucoma have determined the reduction of CSFP in the same way regardless of age patient as demonstrated also by Berdhal et al [7].

Lastly, POAG patients and controls in > 60 age category were characterized by similar reduction of ONSAS.

This result confirms that advanced age and glaucoma disease determine a reduction of CSFP.

The study, conducted by Fleischman et al, found a significant reduction of CSFP after 60 age in normal subjects [17].

Different studies have showed that the age where CSFP started to decline coincided with the age where the prevalence of POAG increased.

The POAG prevalence begins in the 5th and 6th decades and progressively increases through the 8th and 9th decades [18–20].

These data support the hypothesis that reduced CSFP represent a risk factor for progression of POAG and provide an explanation for the mechanism that underlies the age-related increase in the prevalence of POAG.

It has been hypothesized that the choroid plexus that produce CSF within cerebral ventricles undergoes to aging changes determining a reduction of CSF [21–23].

Moreover in plasma of older subjects the levels of vasopressin, a hormone that decrease blood flow of choroid plexus, are increased causing a reduction of CSF production [24,25].

Our study have showed no significant correlation between ONSAS and OCT parameters except between ONSAS and RNFL thickness as confirmed by different studies [15,26].

The changes of GCC and RNFL parameters are the result of a multifactorial pathogenesis that involves not only the reduction of orbital CSFP but also other risk factors such as the ocular blood flow decreased, diabetes, myopia, ethnicity, and genetic background [27–31].

Several studies, as those conducted by Bauerle and Steinborn, reported a good correlation between ultrasound and MRI in measurements of the optic nerve sheath diameter (ONSD) [32,33].

Also Picher et al, revealed no significant difference between the measurements of ONSD in NTG patients performed with CT and those with MRI [34].

Wang et al, using MRI, found that the ONSASW was significantly narrower in NTG than in POAG and control groups at 3, 9 and 15 mm behind the globe. While POAG and control groups did not vary significantly at any of the 3 measurements [35].

While Jaggi et al., using CT scan, showed an increased ONSD in NTG patients compared with controls in prone position [36].

It has been demonstrated that the prone position determines an increased central pressure venous influencing the CSF distribution in the central nervous system [37].

In a recent study conducted by Liu et al., the ONSASW was evaluated by B-scan ultrasound at 3, 5 and 7 mm behind the globe. The ONSASW was significantly narrower in NTG than in

the POAG and controls groups, while there no significant differences between the POAG and control groups [15].

Conversely, Pinto et al. have showed, using B-scan ultrasound, that ONSD was not significantly different between control, NTG and POAG patients [26].

MRI and CT are non-invasive techniques with high spatial resolution but the high costs restrict their wider use as follow-up tools.

The ultrasound assessment of ONSAS is easily available method and cost-effective. It is a non-invasive technique characterized by a robust scan-rescan reproducibility [32].

The evaluation of ONSAS in glaucomatous patients has until recently possible by B-scan ultrasound that does not always performs standard measurements [38,39].

In fact the studies conducted by Liu and Pinto, using B-scan ultrasound have reported different results and a possible explanation could be given by different probe used.

Liu et al. employed a 12 MHz ultrasound probe with a resolution of the ultrasound images higher than the 7.5 MHz probe used in the study of Pinto et al. that may have influenced the accuracy of measurements [15,26].

Moreover the transbulbar sound direction and the incidence of the ultrasound beam on the lamina cribrosa or the dura madre may produce acoustic shadows behind the globe influencing precise measurements [15,40].

Accurate method that provides reliable images of ONSAS measuring can be obtained by the standardized A-scan ultrasound.

It is a simple, sensitive and non-invasive method of detecting and characterizing of ONSAS and allows a real-time examination [41–43].

It is important that sound beam is directed in a perpendicular direction toward the surface of the optic nerve.

When the sound beam incidence is in this position, A-scan ultrasound echograms showed high and perpendicular double spikes that correspond to arachnoidal surfaces [11–13].

The distance between the these two steeply rising surface spikes indicates the maximum arachnoidal diameter in the area scanned by the beam.

To analyze the anterior third of the optic nerve in the point in which are obtained these high and perpendicular double spikes allows to acquire reproducible and repeatable measurements of ONSAS [11,12].

Until now the A-scan ultrasound was used to measure the maximal pial diameter in POAG patients showing a significant reduction compared to controls [44].

Whereas in this study the measurement of ONSAS, using the same tool, have showed a valid and indirect method of CSFP evaluation.

Different studies have showed, using various measurement methods, the close correlation between intracranial pressure (ICP) and ONSD: even slight variations of ICP influences the diameter of the optic nerve [45–51].

In fact, unlike the brain, the optic nerve is not surrounded by a rigid structure, but by orbital fat which is easily compressible.

Thus, any increasing pressure variations of CSF provokes swelling of the optic nerve sheaths owing to the increase in the quantity of internal fluid which subsequently increases the diameter of the optic nerve.

Already in the 1987, Cangemi et al, have showed that the measurement of ONSD by means of A-scan ultrasound provided an immediate evaluation of ICP.

Any increased of CSFP in patients with intracranial hypertension reflected in real time the dilated ONSD also after the surgical treatment when ONSD returned to the normal size showing an immediate reduction of CSFP [52].

The limitation of this study is the relatively small sample size of the groups of patients. Future studies on larger cohorts for each study group are needed to further evaluate the changes of ONSAS in POAG patients.

In conclusion, standardized A-scan ultrasound represents a non-invasive imaging technique with which it is possible to monitor ONSAS changes in glaucomatous patients. The reduction of ONSAS, measured by this tool, confirms the involvement of the lower orbital CSFP in the translaminal pressure gradient that plays an important role in the pathogenesis and progression of POAG.

Supporting information

S1 Table. Measurements of the optic nerve subarachnoid space in glaucoma groups 1 and 2.
(PDF)

Author Contributions

Data curation: Giovanni Cennamo.

Formal analysis: Vincenzo Brescia Morra.

Methodology: Maria Angelica Breve.

Project administration: Gilda Cennamo.

Software: Feliciano Menna.

Writing – original draft: Daniela Montorio.

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