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Research Article

Elevated Aqueous Humour Level of The Collagen Cross-Linking Protein Lysyl-Oxidase-Like-1 (LOXL1) in Primary Open Angle Glaucoma

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Abstract

Purpose: Lysyl-oxidase-like-1 (LOXL1) plays a significant role in pseudoexfoliative glaucoma (PXFG), however its association with primary open angle glaucoma (POAG) is unclear. LOXL1 is a collagen-elastin cross-linking protein which alters the biomechanical properties of the extracellular matrix (ECM) in the trabecular meshwork (TM). Abnormal cross-linking results in TM stiffness, thereby increasing aqueous outflow resistance. In this study, we measured the levels of LOXL1 in the aqueous and serum samples of normal patients and patients with glaucoma (POAG, PXFG and normal tension glaucoma [NTG]).

Methods: Aqueous humour samples were collected from 66 non-glaucoma patients and 31 POAG, 6 PXFG and 11 NTG patients. Serum samples were collected from 28 non-glaucoma patients and 11 POAG, 3 PXFG and 4 NTG patients. We measured the LOXL1 protein concentrations using enzyme-linked immune-sorbent assay (ELISA).

Results: There was significantly higher level of aqueous LOXL1 (ng/mL) in POAG (Median = 22.3, $p = 0.007$) and PXFG (Median = 23.3, $p = 0.02$) compared with non-glaucoma controls (Median = 12.2). Serum LOXL1 (ng/mL) was elevated in PXFG (Median = 79.3, $p = 0.004$) compared with non-glaucoma controls (Median 15.9). There was no difference ($p > 0.05$) in either aqueous or serum LOXL1 in NTG compared with non-glaucoma controls.

Conclusion: We describe an increased aqueous humour (but not serum) level of LOXL1 in POAG.

Keywords: Glaucoma; LOXL1; Cross-linking Proteins

Introduction

Primary open angle glaucoma (POAG) is one of the leading causes of irreversible blindness worldwide [1] and ageing is a known risk factor for developing glaucoma. Ocular tissue stiffness associated with increasing age may also contribute to the pathogenic process of this blinding eye condition [2]. Last et al revealed that stiffness of the human glaucomatous trabecular meshwork (TM) space is 20-fold higher than normal TM indicating that there is impaired aqueous outflow with increased TM stiffness [3]. Increased stiffness of the lamina cribrosa (LC) was also found to be less compliant to changes in stress with increasing age [4]. This may result to an increased susceptibility to permanent deformation of the optic nerve head (ONH), which predisposes to retinal nerve fiber layer damage in POAG.

The human glaucomatous ONH tissue is characterised by extracellular matrix (ECM) remodelling that includes loss of elastin structure [5], increased collagen deposition [6] and elevated transforming growth factor beta-2 (TGFβ-2) and matrix metalloproteinase-2 (MMP-2) [7]. Taking TGFβ as an example, it plays a major role in myofibroblast differentiation and it has been implicated in a number of fibrotic ocular diseases, including glaucoma [8]. Tissue fibrosis occurs when production of ECM by myofibroblasts exceeds the rate of its degradation, resulting in abnormal ECM deposition and alteration in tissue structure [9]. Stimuli including growth factors, tissue injury and oxidative stress promote fibroblasts to proliferate, migrate, and acquire an activated phenotype that leads to its differentiation into myofibroblasts, enhanced ECM production

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and the release of cytokines and growth factors, which in turn results in tissue stiffness and persistent fibrosis [10]. Fibroblast activation is a helpful process in normal tissue repair by producing and remodelling the ECM [11], however, in some cases, prolonged activation becomes uncontrolled, producing a pathological fibrotic response.

Tissue stiffness represents a biomechanical property of an affected tissue. Apart from abnormal fibroblast activation, collagen cross-linking processes within the ECM affects tissues' biomechanical properties by altering its mechanical homeostasis [12]. Tissue stiffness can be defined as the degree to which a tissue resists deformation in response to applied stress (in the form of compression, elongation, or shear force) [13]. The tissue's biomechanical property depends largely on the ECM, where its constituents, such as elastic fibres, fibrillar collagen and glycosaminoglycans (GAGs), are regulated to achieve mechanical balance [14]. Increased collagen crosslinking is observed with increasing age [15] and contributes to the disease process of various systemic conditions including arteriosclerosis, renal, hepatic and pulmonary fibrosis and cancer [16]. Enzymes that cross-link between two proteins, typically between collagen and another ECM constituent such as elastin, are regulated to maintain mechanical homeostasis. Altered cross-linking processes, such as an under- or over-production of a collagen cross-linking protein can result in tissue stiffness, and thus some studies suggest that alterations to the biomechanical properties i.e. stiffness of the TM [3] and LC [17] may have a role in the onset and progression of glaucoma.

One collagen cross-linking protein that has been associated with glaucoma is lysyl oxidase-like-1 (LOXL1). Development of pseudoexfoliative glaucoma (PXFG) is secondary to accumulation of pseudoexfoliative materials (PEX) in the TM, leading to increased outflow resistance and subsequent rise in intraocular pressure (IOP) [18]. This pathogenic process in the eye is a manifestation of an age-related systemic disease – pseudoexfoliation syndrome (PXS), whereby mutation of LOXL1 gene (two single nucleotide polymorphisms (SNPs) - rs1048661 and rs3825942 in Exon 1) results in a higher risk of developing PXFG. LOXL1 enzyme is necessary for tropoelastin crosslinking and elastic fibre formation, maintenance and remodelling [19].

Mutation of the LOXL1 gene leads to a type of stress-induced elastosis associated with excessive production and abnormal aggregation of elastic fibre components and abnormal enzymatic cross-linking processes [18]. LOXL1 genes are expressed in cultured human TM and may contribute to the increased aqueous outflow resistance in glaucoma due to abnormal cross-linking signalling in the ECM [20] or due to chronic accumulation of fibrillar PEX aggregates in the outflow pathways [21] as seen in PXFG.

At present, there is inconsistent association of LOXL1 with POAG. Liu et al did not find any association between the SNPs in LOXL1 with POAG in populations of either Caucasian or West-African individuals [22]. Neither was there an association found for the same LOXL1 SNPs with POAG in a Chinese population [23]. However, there is a genome wide association study (GWAS) in an Asian population that identified seven novel susceptibility loci associated with POAG, which included LOXL1 [24]. Another recent study showed that there was a relationship of polymorphisms rs2165241, rs4886776, and rs893818 in the LOXL1 gene with both PXFG and POAG in a Caucasian population from central Russia [25]. In our study, we aimed to measure the concentration levels of LOXL1 in aqueous and serum samples of non-glaucoma and POAG patients. We also recruited PXFG and normal tension glaucoma (NTG) patients.

Methods And Materials

This was a prospective case-control study, carried out with approval from the institutional research and ethics committee and in accordance to the tenets of the Helsinki declaration. 66 non-glaucoma and 48 patients with glaucoma were recruited into the study. Complete ophthalmic examination including patient history, best corrected logMAR visual acuity, IOP measurement with Goldmann applanation tonometry (GAT), corneal hysteresis (CH) and corneal-compensated IOP (IOPcc) measured by the Ocular Response Analyzer G3 (Reichert Technology), visual field testing with the Humphrey Field Analyzer 3 (Carl Zeiss), and slit lamp examination, including gonioscopy and dilated lens and fundal examination. Non-glaucoma subjects were characterized as patients who had no known ophthalmic conditions identified on examination, with IOP ≤ 21 mmHg and no signs of glaucomatous ONH damage. There were three subgroups of patients with glaucoma, including POAG, NTG and PXFG. POAG was defined as having an untreated IOP was >21 mmHg, an open angle on gonioscopy and characteristic glaucomatous ONH damage with corresponding visual field loss. NTG followed the same criteria as defined for POAG except for having an untreated IOP of ≤ 21 mmHg. PXFG also followed the same criteria as defined for POAG, in addition to having characteristic ocular PEX findings, including PEX material on the anterior lens capsule and pupillary margin. Subjects were excluded if there were any co-existing ophthalmic conditions that would potentially predispose to altered corneal stiffness, such as myopia, previous refractive surgery, and previous corneal diseases. Subjects with a known systemic disease that may predispose to increased collagen cross-linking protein levels were excluded, such as diabetes, active malignancy, cardiovascular disease, and fibrotic diseases including pulmonary, hepatic, or renal fibrosis.

Sample Collection

Aqueous humour samples were collected at the time of cataract surgery using a Rycroft anterior chamber cannula attached to a 1 ml syringe or by using an insulin syringe attached to a 29G needle. Each sample was approximately 30-50 µl in volume. Blood samples were collected during pre-operative cataract assessment clinic using a 3mL EDTA serum tube. The blood sample was then centrifuged at 1000 x g for 15 minutes at room temperature to separate the serum. All samples were then stored in a -80°C freezer until further sample analysis was performed.

Enzyme-Linked Immunosorbent Assay (ELISA)

ELISA was performed on the aqueous and serum samples to measure the concentration of LOXL1. ELISA kits were sourced from MyBioSource (San Diego, USA). Aqueous samples were diluted with 1:4 PBS to bring the sample to a volume sufficient for the ELISA analysis. 100 µl of the samples and standards were added to each well in duplicate and incubated. The samples and standard were removed and 100 µl of a first detecting agent were added and incubated. This same technique was repeated for a second detecting agent. Following this, 90 µl of substrate solution was added to each well and a colour

change to blue was observed in all samples. Stop solution was added and samples were read at 450 nm absorbance. Concentration in ng/mL was calculated by comparing the samples with standard. As the samples are diluted, the concentration is multiplied by the dilution factor.

Statistical Analysis

The distribution of the data was determined using D'Agostino Pearson normality test. The difference in average LOXL1 concentration between controls and glaucoma patients were compared using the non-parametric Mann Whitney test, as the samples have a non-normal distribution. CH and IOPcc followed a normal distribution, therefore t-test was used for comparison of means. For comparison between more than two groups, Kruskal-Wallis test was used to compare the median between the groups. P-value of <0.05 was considered statistically significant. We Used Prism 9, Graphpad Software, Inc. For Our Statistical Analysis.

Results

There were a total of 66 non-glaucoma patients (66 eyes) included in this study with a mean age of 73 ± 7.6 years. 26 were male (40%) and 40 were female (60%). Within the glaucoma group, there were 48 patients included, with 21 (44%) male and 27 (56%) female patients. 31 eyes (65%) within the glaucoma group had POAG, with an average age of 75 ± 8.9 years. 6 eyes had PXFG (12%), with an average age of 76 ± 6.6 years. 11 eyes had NTG (23%), with an average age of 76 ± 7.5 years. Patients with POAG were noted to have significantly lower CH when compared to non-glaucoma patients ($p < 0.0001$). We did not find any significant difference in the mean deviation (MD) values between the glaucoma sub-groups ($p > 0.05$).

Aqueous and Serum LOXL1 Analysis

There was a significant difference in aqueous LOXL1 levels noted ($p = 0.005^{**}$) among the four study groups, with PXFG and POAG having the highest, and almost similar LOXL1 aqueous levels. Patients with POAG had significantly raised LOXL1 aqueous levels when compared to non-glaucoma patients ($Median_{POAG} = 22.3$ ng/ml vs $Median_{non\text{-}glaucoma} = 12.2$ ng/ml, $p = 0.007^{**}$). Similarly, the median LOXL1 aqueous levels in patients with PXFG was significantly higher than non-glaucoma patients ($Median_{PXFG} = 23.2$ ng/ml vs $Median_{non\text{-}glaucoma} = 12.2$ ng/ml, $p = 0.02^{*}$). We did not find any significant difference in the aqueous LOXL1 levels between POAG and PXFG ($Median_{POAG} = 22.3$ ng/ml vs $Median_{PXFG} = 23.2$ ng/ml, $p = 0.48$) or between NTG and non-glaucoma ($Median_{NTG} = 14.9$ ng/ml vs $Median_{non\text{-}glaucoma} = 12.2$ ng/ml, $p = 0.61$).

In comparison to the aqueous samples, we recruited a smaller number of patients for serum LOXL1 analysis. There were 28 non-glaucoma controls, 11 patients with POAG, 3 patients with PXFG, and 4 patients with NTG included for serum LOXL1 measurements.

Patients with PXFG had significantly elevated serum LOXL1 levels when compared to POAG ($Median_{PXFG} = 79.3$ ng/mL vs $Median_{POAG} = 29.1$ ng/mL, $p = 0.006^{**}$) and non-glaucoma controls ($Median_{PXFG} = 79.3$ ng/mL vs $Median_{non\text{-}glaucoma} = 15.9$ ng/mL, $p = 0.0004^{****}$) respectively. Serum LOXL1 levels of PXFG patients were found to be 4.9 times higher than the non-glaucoma control group. Although the serum LOXL1 in patients with POAG ($Median_{POAG} = 29.1$ ng/mL, $p = 0.18$) and NTG ($Median_{NTG}$ 47.1 ng/mL, $p = 0.12$) were almost two and three times higher than non-glaucomacontrol group, this was found to be non-significant. Table 2 summarizes the LOXL1 levels in aqueous and serum samples for each study group.

We also performed correlation analysis between aqueous and serum LOXL1 for non-glaucoma and glaucoma groups, and in patients with POAG (Table 3). There was no significant correlation found between these two variables for any of the groups, however we note a borderline significance in the non-glaucoma group for the relationship between aqueous and serum LOXL1 ($p = 0.07$).

Table 1: Summary of patient demographics including age, gender, corneal hysteresis and mean deviation values. Median mean deviation and corneal hysteresis values between the glaucoma sub-groups did not show any significant differences ($p > 0.05$).

	NON-GLAUCOMA	POAG	PXFG	NTG
Age (Mean ± SD, years)	73 ± 7.6	75 ± 8.9	76 ± 6.6	76 ± 7.5
Gender (M:F)	26:40	15:16	2:4	4:7
	NORMAL (n = 18)	**POAG (n = 15)**	**PXFG (n = 4)**	**NTG (n = 8)**
Corneal hysteresis [IQR] (mmHg)	11.5 [10.1, 11.9]	9.0 [8.1, 9.7]	8.7 [6.5, 10.9]	9.9 [9.2, 10.9]
		POAG (n = 28)	**PXFG (n = 6)**	**NTG (n = 11)**
Mean deviation [Interquartile range, IQR] (db)		-11.2 [-7.8, -15.3]	-10.8 [-5.3, -17.4]	-12.9 [-10.5, -14.5]

Table 2: Summary of the LOXL1 levels in aqueous and serum samples for non-glaucoma, POAG, PXFG and NTG patients.

	AQUEOUS LOXL1 levels (ng/ml)			
	Non-glaucoma (n = 66)	**POAG (n = 31)**	**PXFG (n = 6)**	**NTG (n = 11)**
Age (Mean ± SD, years)	73 ± 7.6	75 ± 8.9	76 ± 6.6	76 ± 7.5
Gender (M:F)	26:40	15:16	2:4	4:7
Median [IQR](ng/mL)	12.2 [4.8, 24.6]	22.3 [11.1, 37.7]	23.3 [18.2, 68.2]	14.9 [13.0, 18.6]
	SERUM LOXL1 levels (ng/ml)			
	Normal (n = 28)	**POAG (n = 11)**	**PXFG (n = 3)**	**NTG (n = 4)**
Age (Mean ± SD, years)	75 ± 7.8	70 ± 7.7	73 ± 2.9	74 ± 6.2
Gender (M:F)	15:13	8:3	1:2	0:4
Median [IQR](ng/mL)	15.9 [7.3, 30.7]	29.1 [16.5, 43.6]	79.3 [76.9, 87.8]	47.1 [22.2, 56.0]

Table 3: Correlation analysis between aqueous and serum LOXL1 in non-glaucoma, glaucoma and POAG groups did not identify any significant relationship between the two variables.

Correlation analysis Aqueous-Serum LOXL1	**Non-glaucoma (n = 24)**	**Glaucoma (n = 18)**	**POAG (n = 11)**
	r = 0.38, p = 0.07	r = 0.22, p = 0.36	r = 0.44, p = 0.18

Discussion

Our study found a significantly higher LOXL1 level in aqueous humour (but not serum) samples of patients with POAG compared to non-glaucoma patients. CH was significantly lower in all glaucoma subgroups compared to non-glaucoma controls ($p < 0.05$). Both aqueous and serum LOXL1 levels in the PXFG group were noted to be significantly raised when compared to normal patients. We did not find any significant difference in either aqueous or serum LOXL1 between NTG and non-glaucoma patients.

The main highlight of our study is the significantly higher aqueous level of LOXL1 in patients with POAG when compared to non-glaucoma controls (Median $AqLOXL1_{POAG}$ = 22.3 [11.1, 37.7] ng/ml versus Median $AqLOXL1_{non\text{-}glaucoma}$ = 12.2 [4.8, 24.6] ng/ml, p-value = 0.007**). Furthermore, the median value was relatively similar to patients with PXFG (Table 2). The pathological mechanism of LOXL1 in POAG may differ than in PXFG. In contrast to accumulation of PEX materials in the TM in PXFG, it is most likely that the potential role of LOXL1 in POAG is through a multifactorial TM environment that leads to dysregulation of its usual functions. The initiation of abnormal ECM processes can be triggered by several pathogenic factors, such as anterior chamber hypoxia, oxidative stress, pro-inflammatory processes involving cytokines, and elevated TGFβ2. These factors have been shown to cause up-regulation of LOXL1 and elastic components either by direct or secondary mediators [20]. Additionally, cyclic mechanical stretch has been suggested to play an important role in IOP homeostasis by modulating the TM cells' response to prolonged strain/stretch associated with increased IOP [26]. Youngblood et al identified 219 mRNAs, 42 microRNAs, and 387 long non-coding (lnc)RNAs with differential expression in TM cells upon cyclic mechanical stretch, with significant enrichment of genes involved in steroid biosynthesis, glycerolipid metabolism, and extracellular matrix-receptor interaction [27].

The search for an association between LOXL1 and POAG is still in progress. As previously mentioned, analysis of LOXL1 gene polymorphism in POAG patients seems to bring inconsistent results. There are also a limited number of investigative studies that measure the concentration levels of LOXL1 (or other LOX family members) in the aqueous humour of glaucoma patients. A study by Zadravec et al supports our findings of elevated LOXL1 levels in the aqueous humour within the anterior chamber. They found that in transgenic mice with ocular overexpression of LOXL1, its lens, ciliary zonules and retina contained high levels of LOXL1, which indicates the transgenic lens can secrete soluble LOXL1 into the extracellular space [28]. However, in comparison to knock-out mice that lacks LOXL1, disruption of the blood-aqueous barrier and lens abnormalities were found, and it was also suggested that both LOXL1 and a compromised blood–aqueous barrier could be required for producing macromolecular deposition and glaucoma [29].

It is well known that LOXL1 has been associated with PXS and PXFG. LOXL1 is a major component of PEX deposits within the TM, which is paralleled with an upregulation of other ECM constituents such as fibrillin-1, fibulin-4, LTBP-1, LTBP-2 and tropoelastin [21]. Accumulation of these PEX deposits consequently leads to secondary glaucoma due to increased aqueous outflow resistance. LOXL1 has been localized in the eyes of patients with PXS. A significantly higher mRNA and protein expression of LOXL1 levels are found in the TM and other anterior segment structures, including the iris and ciliary body at early stages of PXS [30], however LOXL1 expression is reduced in the later stages of PXFG.

Although the sample size for this study group of patients with PXFG was small (Aqueous $LOXL1_{PXFG}$, n = 6 and Serum $LOXL1_{PXFG}$, n = 3), we found that this group of patients had the highest LOXL1 levels in both aqueous and serum samples when compared to normal (Table 2). These findings agreed with other studies that confirms the elevated expression level of LOXL1 within the anterior chamber structures in PXFG [30,31]. Higher serum LOXL1 levels in our PXFG patients also corroborates the extra-ocular or systemic involvement in PXS [32,33].

Most studies have focused on the genetic association of LOXL1 with PXFG. Our research group recently reported increased LOXL1 concentration found in the aqueous of patients with PXFG when compared to controls [34]. This study found a decreased LOXL1 expression in human tenon's capsule fibroblasts in PXFG patients, and this appears to be related to an increased global DNA methylation level [34]. There are studies that suggest LOXL1 is associated with an increased genetic risk of POAG. A recent GWAS in an Asian population identified seven novel susceptibility loci associated with POAG, including LOXL1 [35]. Another recent study found that the same LOXL1 gene polymorphisms in PXFG (rs2165241, rs4886776, and rs893818) were also contributing to POAG for a Caucasian population in central Russia [25]. However,other studies found a lack of association of the LOXL1 variants or polymorphism with POAG in Caucasian, African-American and Ghanian populations [22], or in a Chinese population [23].

Serum LOXL1 has not been previously investigated in POAG. Our study did not find a significant difference between non-glaucoma patients and the POAG group (Table 2), however we found that serum LOXL1 was 2.7 times higher in patients with PXFG when compared to POAG ($Median_{PXFG}$ = 79.3 ng/ml vs $Median_{POAG}$ = 29.1 ng/ml, p = 0.006), supporting the systemic nature of PXFG. In addition, we also found a borderline significance in the correlation between aqueous LOXL1 and serum LOXL1 in non-glaucoma patients (r = 0.38, p = 0.07, n = 24). Gayathri et al examined aqueous and serum LOXL1 activity in a South Indian population with PXFG, and in contrast to our results, they found significantly lower aqueous levels of LOX in patients with PXFG compared to controls, and also found a negative correlation between LOX activity and TGF-β1 and TGF-β2 in the aqueous humour [36]. We did not find a significant association between aqueous and serum LOXL1 in the POAG group (r =0.44, p = 0.18, n =11), however our sample size was small. Serum levels of LOXL family members have been implicated in the pathology of cancer and fibrotic disease(s). For example, LOXL2 is associated with hepato-cellular carcinoma [37] and liver fibrosis [38]. The LOXL1/elastin relationship has also shown to be relevant in fibrosis progression or when reaching end-stage liver cirrhosis processes [39].

The main limitation of this study is our small sample size in the PXFG and NTG groups. Therefore, some of our results may have not reached statistical significance, especially for the interpretation of mean or median comparison analysis for glaucoma diagnosis groups with smaller numbers, such as in the PXFG and NTG groups. Of interest, despite the small sample size and lack of statistical

significance, we did not find any difference in aqueous LOXL1 levels for the NTG group compared to the non-glaucoma group ($Median_{NTG}$ = 14.9 ng/ml vs $Median_{non\text{-}glaucoma}$ = 12.2 ng/mL vs, p = 0.61), while higher serum levels were noted in the NTG group compared to the non-glaucoma gropup ($Median_{NTG}$ 47.1 ng/ml vs $Median_{non\text{-}glaucoma}$ = 15.9 ng/mL, p = 0.12). This finding may provide a future direction to investigate any relationship between raised serum LOXL1 with ONH vascular perfusion insufficiency and the role in keeping the IOP within the normal range for patients with NTG.

In conclusion, our current study identified a significant finding of increased aqueous humour levels of the collagen cross linking protein LOXL1 in POAG. The potential LOXL1-related mechanism that leads to an increased aqueous outflow resistance in patients with POAG is more likely due to a multi-factorial TM environment that induces TM and ECM fibrosis and stiffness. The true role of altered collagen cross-linking processes that causes increased ocular stiffness requires further investigation, which if found to be relevant could provide a novel therapeutic strategy in the future management of glaucoma.

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