The Pathophysiology of Sleep Apnea and its Association with Changes in Systemic and Ocular Elastin

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Introduction

Culbertson and Tseng first reported on floppy eyelid syndrome (FES) in 1981, and describe a syndrome of rubbery, lax upper eyelids with tarsal papillary conjunctivitis seen in young obese men[1,4,5]. Previous studies have reported the histopathology and proposed pathophysiology of the eyelid laxity[5,6]. Loss of elastin fibers in eyelid tissue was a characteristic finding.[5,6]. Schlotzer-Schrehardt et.al report in their paper discussing the pathophysiology of elastin degradation that residual elastin fibers in patients with FES demonstrated abnormal ultrastructure and diminshed elastin core and based on the immunohistochemical analysis, and increased presence of degradative enzymes, notably matrix metalloproteinases 2, 7, 9 and 12[6].

Obstructive sleep apnea syndrome (OSAS) is characterized by interruption of ventilation for more than 10 seconds due to airway collapse[8]. The cause of this disorder has been related to obesity, increase in neck circumference and increase in the size of the soft palate and tongue.[6] The exact explanation for the changes in the soft palate and tongue is unclear but some reports demonstrate a decrease in elastin in the soft palate and uvula tissue[9]. Series et. al analyzed in their study the amount of immune cells, collagen, and elastic fiber network integrity in patients with and without obstructive sleep apnea. The paper describes an increase in immune cells of patients with OSA, as well as an increase in elastic fiber disorganization and a direct relationship between elastic fiber network disorganization and the apnea-hypopnea index[9].

Woog first reported the association of FES and OSAS. OSA is one of the most well known systemic associations of FES[8]. In patients with FES, there is an upregulation of vascular endothelial growth factor (VEGF), a substance that increases new blood vessel growth and is induced by the hypoxia (lack of oxygen) caused by the OSA[16,17].

The purpose of this study is to compare the elastin in normal patients with those with OSA in a variety of tissues including: the eyelid, skin, optic nerve, orbit and soft palate. We will also measure the levels of VEGF and assess the degree of vascularization in the same tissues. The hypothesis is that OSA, and the resultant lack of oxygen, leads to a generalized increase in inflammation including enzymes that digest elastin, as well as new blood vessel growth.

Objectives

Hypothesis I: Sleep apnea is a complex multi-organ/tissue disease associated with chronic intermittent hypoxia that results in inflammatory changes associated with a loss or disruption of elastin.

OBJECTIVE I: Compare amounts of elastin in normal patients and in patients with OSA in the following tissues:
- eyelid
- skin
- soft palate and uvula
- orbit
- optic nerve

Hypothesis II: Chronic intermittent hypoxia in OSA will stimulate the production of VEGF and lead to new blood vessel growth[16,17.]

OBJECTIVE II: Measure the presence of VEGF in the following tissues:
- eyelid
- skin
- soft palate and uvula
- orbit
- optic nerve

Methods

Soft Palate and Uvula

1) Search will be done for uvulopalatopharyngoplasties (UPPP) performed at Loyola using CPT code 42145.
   a) Determining whether patients with resected uvulas and soft palates were obese and/or had OSA.
2) Search will be done on Loyola pathology database for uvula and soft palate resected due to obstructive sleep apnea.
3) Examination procedures:
   a) Paraffin blocks will be retrieved, cut and stained with hematoxylin and eosin and elastin stain (Verhoeff-Van Gieson stain) to determine morphology and contents of elastin.
   b) VEGF immunohistochemical stain will also be examined in the same tissue.

Orbit, and Optic Nerve

1) We will obtain eyelid, orbit, and optic nerve specimens from Eversight Eye bank.
2) Eye bank will provide two specimens from obese OSA patients and two specimens from non-obese, non-OSA patients, our controls.
3)Tissue samples will be assessed for elastin contents and expression of VEGF
4) Examination procedures:
   a) Eversight eye bank specimens will be preserved in formalin and sent to Loyola for study and examination.
   b) Paraffin blocks will be retrieved, cut and stained with hematoxylin and eosin and elastin stain (Verhoeff-Van Gieson stain) to determine morphology and elastin contents.
   c) VEGF immunohistochemical stain will also be performed in the same tissue

Skin

1)We will obtain skin specimens from obese patients with presumed OSA that will undergo bariatric surgery. These patients will be enrolled in another clinical study at Loyola (LU Number: 207399).
2)Specimens from non-obese, non-OSA patients will serve as our controls.
3) Skin samples will be assessed for elastin and VEGF .
4) Examination procedures
   a) Paraffin blocks will be retrieved and stained for hematoxylin and eosin and elastin stain (Verhoeff-Van Gieson stain) to determine morphology and elastin contents.
   b) VEGF immunohistochemical stain will also be examined in the same tissue.

*Semi-quantitative measurement of elastic fiber content will be performed using color slides taken from sections stained with Von Gieson's stain. Slides will be projected onto a screen at 30x magnification. The Von Gieson-stained elastic fibers will be transferred to a sheet of paper and measured by planimetry, as described by Schlötzer-Schrehardt et al.[6] Statistical comparison of mean values of elastic fiber area will be performed for obese, OSA specimen and control specimen.

Results

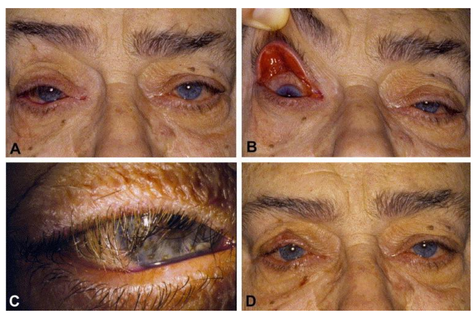
This is an ongoing study. Results pending conclusion of study.

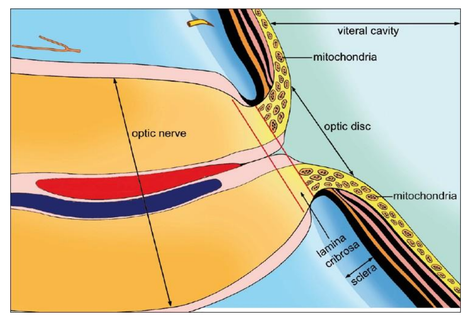
Inclusion criteria:

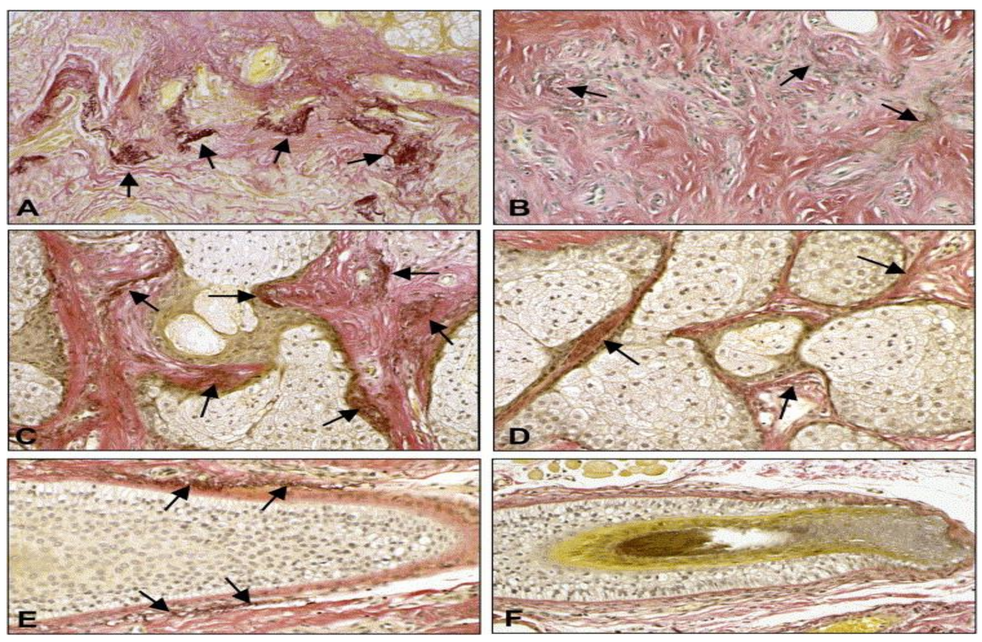
1) Patients undergoing gastric bypass procedures who consent to provide a skin biopsy.
2) Patients with history of prior uvulopalatopharyngectomy.
3) Eye bank provided posterior globes with optic nerve in deceased patients with a history of obesity and/or sleep apnea.
4) Controls for this study will be:
   a. Posterior globes and optic nerve from patients with no history of obesity and OSA.
   b. Uvulopalatopharyngectomy specimens from patients that did not have sleep apnea.
   c. skin specimens from the pathology database that were normal tissue.

Exclusion criteria:

Live patients.







Light Microscopy of eyelid sections in Van Gieson stained for elastic fibers in FES (B,D,F) and control specimen (A,C,E) [6.] Dark brown is elastin, Red is collagen.

Conclusion

This is an ongoing study. Results and conclusion pending.

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