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MAIN ARTICLE

Risk factors for adult acquired subglottic stenosis

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Abstract

Objective: The aetiology and outcomes for patients with acquired subglottic stenosis are highly variable. This study aimed to identify risk factors for subglottic stenosis and patient characteristics that predict long-term clinical outcomes.

Methods: A retrospective review was performed on 63 patients with subglottic stenosis and 63 age-matched controls. Patient demographics and clinical characteristics were compared. Subglottic stenosis patients were further grouped according to tracheostomy status (i.e. tracheostomy never required, tracheostomy initially required but patient eventually decannulated, and tracheostomy-dependent). Patient factors from these three groups were then compared to evaluate risk factors for long-term tracheostomy dependence.

Results: Compared to controls, patients with subglottic stenosis had a significantly higher body mass index (30.8 *vs* 26.0 kg/m^2; $p < 0.001$) and were more likely to have diabetes (23.8 per cent *vs* 7.94 per cent; $p = 0.01$). Comparing tracheostomy outcomes within the subglottic stenosis group, body mass index trended towards significance ($p = 0.08$). Age, gender, socio-economic status, subglottic stenosis aetiology and other co-morbidities did not correlate with outcome.

Conclusion: Obesity and diabetes are significant risk factors for acquiring subglottic stenosis. Further investigations are required to determine if obesity is also a predictor for failed tracheostomy decannulation in subglottic stenosis.

Key words: Laryngostenosis; Inflammation; Obesity; Tracheostomy; Diabetes Mellitus

Introduction

The aetiology and clinical course of subglottic stenosis are highly variable. The current most common cause of subglottic stenosis is iatrogenic trauma from intubation or tracheostomy.[1] It has been estimated that there are 4.9 cases of post-intubation subglottic stenosis per million per year in the general population.[2] Among intubated patients, incidence ranges from 1 per cent to 11 per cent, with only 1–2 per cent with severe enough stenosis to become symptomatic.[3] The factors that cause severe stenosis in some patients are poorly understood.

Management of subglottic stenosis is a challenge for otolaryngologists as the treatment algorithm continues to evolve. Medical management strategies include systemic or inhaled steroids, antibiotics, and reflux medications. Surgical management options include open surgery and endoscopic methods, with widespread debate regarding when to utilise different surgical techniques.[1,4–6] Inadequacies of these strategies often lead to multiple, repeated surgical procedures, and cause patients with severe subglottic stenosis to remain tracheostomy-dependent.

This study aimed to identify risk factors for developing subglottic stenosis and determine if there were patient characteristics that could serve as prognostic indicators of clinical outcomes in this patient population. Determination of prognostic indicators could then allow more personalised treatment strategies and expectations, optimising outcomes and minimising morbidity.

Materials and methods

The study group consisted of patients with a diagnosis of subglottic stenosis who were managed in the laryngology clinic of the Hospital of the University of Pennsylvania's Department of Otorhinolaryngology –

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Head and Neck Surgery between 1 January 2009 and 31 December 2012. Inclusion criteria were: an age of 18 years or older, a diagnosis of subglottic stenosis and adequately complete medical records. This study was approved by the Institutional Review Board at the Hospital of the University of Pennsylvania (protocol number 816268). Written consent was obtained from all participants.

A retrospective chart review was performed on patients meeting the inclusion criteria. Age-matched controls were recruited from the same laryngology practice (these individuals had complaints other than subglottic stenosis). Extracted data included demographic information (age, gender and race) and co-morbidities (body mass index (BMI), gastroesophageal reflux disease, diabetes mellitus and American Society of Anesthesiologists' physical status classification (as a measure of overall health)). Analysed factors included: the number of procedures required by each patient, the need for a tracheostomy, the ability to decannulate and the time to decannulation.

Patient demographics and clinical characteristics were compared using an unpaired *t*-test, with significance set at $p < 0.05$. Binary data were evaluated using a chi-square test for significance. Analysis of variance was performed to compare the three subsets of subglottic stenosis patients (i.e. tracheostomy status groups: tracheostomy never required, tracheostomy initially required but patient eventually decannulated, and tracheostomy-dependent).

Results

Sixty-three patients with subglottic stenosis were identified who met our inclusion criteria. Forty patients never required a tracheostomy, 15 had a tracheostomy but were successfully decannulated, and 8 patients remained tracheostomy-dependent at last follow up.

Compared to controls, patients with subglottic stenosis had a significantly higher BMI (30.8 ± 8.77 kg/m^2 *vs* 26.0 ± 5.75 kg/m^2; $p < 0.001$) and were more likely to have diabetes (23.8 per cent *vs* 7.94 per cent; $p = 0.01$) (Table I). Additional analysis demonstrated no significant difference in the percentage of subglottic stenosis patients with diabetes that were obese (BMI $\geq$ 30 kg/m^2) and not obese (BMI $<$ 30 kg/m^2) (53.33 per cent and 46.67 per cent, respectively; $p = 0.612$).

When comparing patients within the subglottic stenosis group who never underwent tracheostomy with those who did, BMI approached significance ($p = 0.08$). Patients who remained tracheostomy-dependent had significantly higher BMIs compared to the combined group of patients who never required tracheostomy and those that were decannulated (36.6 ± 11.9 kg/m^2 *vs* 29.9 ± 11.8 kg/m^2; $p = 0.044$).

Age, gender, socio-economic status, subglottic stenosis aetiology, number of procedures, gastroesophageal reflux disease, diabetes mellitus and other co-morbidities were not found to correlate with outcome (Table II).

Discussion

Mechanical trauma is a well-established cause of subglottic stenosis; however, only a very small percentage of patients who undergo endotracheal intubation go on to develop subglottic stenosis. Our data demonstrate that obesity (BMI $\geq$ 30 kg/m^2) and diabetes are patient-specific factors that potentially contribute to the development of subglottic stenosis. To our knowledge, no other literature exists implicating a role for obesity in acquired subglottic stenosis.

The underlying pathophysiology of subglottic stenosis is currently understood to be a process of abnormal wound healing and subsequent proliferation of granulation tissue.[7] Animal models of subglottic stenosis have demonstrated an upregulation of inflammatory markers including transforming growth factor beta and interleukin 1.[8,9] This observation has been reproduced with human subglottic granulation tissue by various researchers.[10–13] In fact, Puyo and Dahms demonstrated significant tracheal inflammation (a 10-fold increase in polymorphonuclear cells) after short-term intubation in otherwise healthy patients.[13]

If we accept that subglottic stenosis is the result of persistent pathological inflammation, then our findings are not surprising. It is well established throughout the scientific literature that obesity triggers a chronic inflammatory state that promotes the production of pro-inflammatory markers.[14] Patients with chronic inflammatory states such as obesity may be more susceptible to laryngotracheal injury. Moreover, once established, laryngotracheal injuries may be harder to manage, as suggested by the trend towards significance for tracheostomy outcomes in this study. Nevertheless,

TABLE I
CLINICAL CHARACTERISTICS OF ALL SUBJECTS

Characteristic	Subglottic stenosis patients*	Controls†	*p*
Age (mean (SD); years)	54.14 (17.34)	56.60 (14.23)	0.39
Gender (% female)	68	56	0.14
BMI (mean (SD); kg/m^2)	30.84 (8.77)	26.04 (5.75)	<0.001‡
Diabetes mellitus (*n* (%))	15 (23.81)	5 (7.94)	0.01‡
GORD (*n* (%))	32 (50.79)	34 (53.97)	0.72

*$n = 63$; †$n = 63$. ‡Indicates statistical significance. SD = standard deviation; BMI = body mass index; GORD = gastroesophageal reflux disease

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TABLE II
CLINICAL CHARACTERISTICS OF PATIENTS WITH SUBGLOTTIC STENOSIS BY TRACHEOSTOMY STATUS

Characteristic	Tracheostomy status			*p*
	Never required*	Decannulated†	Dependent‡	
Age (mean (SD); years)	51.12 (17.35)	58.4 (18.23)	61.25 (13.16)	0.18
Gender (% female)	70	80	37.5	0.11
BMI (mean (SD); kg/m^2)	29.24 (7.95)	32.01 (8.18)	36.55 (11.85)	0.08
Diabetes mellitus (%)	22.5	20	37.5	0.62
GORD (%)	55	46.67	37.5	0.63

*$n = 40$; †$n = 15$; ‡$n = 8$. SD = standard deviation; BMI = body mass index; GORD = gastroesophageal reflux disease

further analysis with an adequately powered study is necessary before drawing these conclusions.

As with obesity, chronic inflammation has been shown to play a significant role in diabetes mellitus and its sequelae.[15] It is therefore not surprising that our data and other studies[16,17] have demonstrated that diabetes mellitus was more common in the subglottic stenosis patients than the controls; although, our study showed no correlation between diabetes and tracheostomy status. A 2007 review by Ettema *et al.* showed the presence of diabetes to be associated with more severe stenosis: diabetes was diagnosed in 5.3 per cent of patients with Myers Cotton grade I or II stenosis compared to 36.4 per cent of patients with grade III or IV stenosis.[16] Another review, by Sinacori *et al.*, demonstrated the impact on clinical course, showing that subglottic stenosis in diabetic patients did not recur more than in non-diabetics, but the time to recurrence in diabetic patients was significantly shorter.[17] More recently, a study by Tawfik *et al.* demonstrated that patients with diabetes were at an increased risk for decannulation failure after laryngotracheal reconstruction.[18]

- **Subglottic stenosis is most commonly caused by trauma following intubation**
- **Subglottic stenosis development is thought to be due to abnormal wound healing and granulation tissue proliferation**
- **Patient-specific factors that contribute to its development may relate to chronic inflammation, as with laryngopharyngeal reflux**
- **This study demonstrates that two systemic chronic inflammatory states, obesity and diabetes, are risk factors for subglottic stenosis**
- **Tracheostomy decannulation outcomes in subglottic stenosis may be influenced by body mass index**

Laryngopharyngeal reflux (LPR) is another co-morbidity widely believed to contribute to subglottic stenosis, though this remains somewhat controversial.[19–21] We did not find the presence of LPR to play a significant role for our patients, but this is likely in part a result of our study design. The presence of LPR was assumed if the patient was on anti-reflux medication. Most subglottic stenosis patients in our practice are placed on anti-reflux medications as part of their management strategy, so, in the absence of pH testing, we cannot define who truly had extraesophageal reflux and LPR. Furthermore, as our controls are also laryngology patients, they are more likely to be placed on anti-reflux medications than the general population.

This retrospective chart review is subject to the limitations encountered in similarly designed studies. It is important to understand that the association between obesity or diabetes and subglottic stenosis does not imply a causal relationship, but instead may be the result of independent variables that commonly occur together. Additional limitations in this study include the presence of potential confounding variables in the analysis such as diabetes and obesity; however, supplementary analysis suggested that the obese and non-obese groups did not have significantly different numbers of diabetic patients. Similarly, obesity status itself could have been a cause for delay in tracheostomy decannulation, ultimately resulting in subglottic stenosis from prolonged intubation. The data that can be extracted from a chart review are directly dependent on the quality of medical documentation. One particular limitation in this study is the small sample size of patients with subglottic stenosis, particularly the imbalance of subject numbers when the subglottic stenosis patients were divided into groups based on tracheostomy status. Only 9 patients were tracheostomy-dependent while 40 never required a tracheostomy. This could explain why differences in BMI approach but do not reach significance.

Conclusion

Obesity and diabetes are both conditions that alter the inflammatory profile and thus impact a patient's ability to heal after injury. The development and persistence of subglottic stenosis is one example of this phenomenon. Further studies with a larger cohort of patients and a prospective design are needed. Additionally, studies examining the effects of weight loss and strict glucose control in patients with subglottic stenosis could reveal these to be attractive opportunities for managing this complex disease.

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