The role of local expression of hormone receptors in the genesis of idiopathic tracheal stenosis

Johannes Schweipert[1,2#^], Carina Riediger[2#], Jan Erik Balandat[3], Viktor Bonkowsky[4], Christoph Kahlert[2], Dietmar Kraus[1]

[1]Department of General, Visceral and Thoracic Surgery, Klinikum Nuremberg, Nuremberg, Germany; [2]Department of Visceral, Thoracic and Vascular Surgery, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; [3]Department of Pathology, Klinikum Nuremberg, Nuremberg, Germany; [4]Department of Ear, Nose and Throat Surgery, Klinikum Nuremberg, Nuremberg, Germany

Contributions: (I) Conception and design: J Schweipert, C Riediger, D Kraus, V Bonkowsky, JE Balandat; (II) Administrative support: All authors; (III) Provision of study materials or patients: J Schweipert, D Kraus, V Bonkowsky, JE Balandat; (IV) Collection and assembly of data: J Schweipert, D Kraus, V Bonkowsky, JE Balandat; (V) Data analysis and interpretation: J Schweipert, C Riediger, D Kraus, C Kahlert; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

#These authors contributed equally to this work.

Correspondence to: Dr. med. Johannes Schweipert, MHBA. Department of Visceral, Thoracic and Vascular Surgery, University Hospital Carl Gustav Carus, Technische Universität Dresden, Fetscherstraße 74, 01307 Dresden, Germany; Department of General, Visceral and Thoracic Surgery, Klinikum Nuremberg, Nuremberg, Germany. Email: Johannes.Schweipert@uniklinikum-dresden.de.

Background: Tracheal stenosis in adults is usually the result of mechanical injuries either from direct trauma, tracheotomy or intubation. Idiopathic stenosis in the cricotracheal section is a rare condition and occurs almost exclusively in females. Therefore, an influence of the female sexual hormones estrogen and progesterone has been assumed previously.

Methods: Tracheal specimens of 27 patients who received tracheal resection for either idiopathic tracheal stenosis (ITS) (n=11) or posttraumatic tracheal stenosis (PTTS) (n=16) between 2008 and 2019 in our surgical department were included and retrospectively analyzed. Immunohistochemical staining of tracheal specimens concerning the hormone receptor status of progesterone and estrogen was performed.

Results: While post-tracheotomy stenosis occurred in males (n=6) as well as in females (n=10), none of the patients with idiopathic stenosis were males. All of the idiopathic stenosis (n=11; 100%) showed a strong expression of the estrogen receptors (ERs) in the fibroblasts and expression of progesterone receptors (PRs) in fibroblasts in 8 of 11 (72.7%). In the post-tracheotomy patients, only 3/16 (18.8%) showed slight staining of PRs and 6/16 (37.5%) of ERs. Of those, only one male patient presented with expression of ERs and PRs and another male patient presented with isolated PRs. Oral intake of hormone compounds was seen in 11/27 (40.7%) patients: 7/11 (63.6%) in the ITS group and 4/16 (25%) in the PTTS (noteworthy that the PTTS group included 6 male patients).

Conclusions: Although the number of patients is small, our results show that the expression of female sexual hormone receptors in the fibroblasts of the trachea is a persistent finding in ITS. Surgery provided good results with a favorable long-term outcome without recurrence of stenosis for ITS and PTTS. Further investigation with a special focus on hormones is needed to assist in the prevention of this rare disease.

Keywords: Idiopathic tracheal stenosis (ITS); estrogen receptor expression; progesterone receptor expression; tracheal resection

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^ ORCID: 0000-0002-8488-3087.

Introduction

Laryngotracheal or tracheal stenosis in adults is a rare condition that can be located below the glottis and the first two tracheal rings (subglottic stenosis), the upper and the lower trachea (1). Many patients get misdiagnosed for asthma, chronic obstructive pulmonary disease (COPD) and gastroesophageal reflux disease (GERD). Consequently, diagnosis is often delayed ranging from 19 months to 4 years. The McCaffrey classification differentiates 4 stages of subglottic stenosis according to localization and length of stenosis while Myer-Cotton classifies 4 grades according to obstruction of the airway (2,3). According to underlying etiology, tracheal stenosis can be classified as post-traumatic, inflammatory, neoplastic or idiopathic. Most post-traumatic conditions are trauma from intubation, surgery or radiation. Posttraumatic tracheal stenoses (PTTS) have a reported incidence of 10–22% of all long term intubated patients, but only 1–2% of patients develop symptoms (4). Inflammatory processes leading to tracheal stenosis can be based on autoimmune processes as vasculitis or infectious diseases. Rarely, congenital stenoses of the subglottic area are described as well as neoplastic disorders as adenoid cystic carcinoma, mucoepidermoid carcinoma and squamous cell carcinoma. Idiopathic subglottic or tracheal stenoses (ITS) occur in absence of any traumatic, inflammatory or neoplastic process. Only 5% of all subglottic/tracheal stenoses are called idiopathic with an estimated incidence of 1:400,000. Interestingly, ITS seems to almost exclusively affect women with a median age between 30 and 50 years

(5-8). ITS is affecting mostly the subglottic area (9). Some authors suspect association with female hormones. Estrogen receptor (ER) and progesterone (PR) were identified in fibroblasts of the scar tissue creating the stenosis in these patients (10-12).

The aim of this study was to investigate all patients surgically treated for tracheal stenoses in our department, with a special focus on hormone receptors. All tissue samples were re-analyzed for ER and PR status. Comparative analysis between ITS and PTTS was performed. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1687/rc).

Methods

Study design

The current study was designed as a retrospective, single-center analysis comparing ITS and PTTS as control group.

Patient selection

All patients receiving tracheal resection for tracheal stenosis in the Department of General, Visceral and Thoracic Surgery, Klinikum Nuremberg between 2008 and 2019 were included. Patients with malignant or neoplastic tracheal stenosis were excluded from this analysis as well as distal tracheal resections. Since we do not treat patients under the age of 16 in our department, no pediatric patients were included in our case series. Patients' characteristics were reviewed as well as comorbidities, intake of hormone compounds, preoperative interventions and perioperative outcome. Stored tissue samples of tracheal specimens were re-analyzed with a special focus on hormone receptors.

Diagnostics and surgical treatment

All patients were diagnosed by preoperative laryngo-tracheo-bronchoscopy and a computed tomography (CT) scan to determine length, localization and grade of the tracheal stenosis. Blood tests of antinuclear antibodies (ANAs) and anti-neutrophil cytoplasmatic antibodies (ANCAs) were not routinely performed. Due to the retrospective study design, neither levels of estrogen and progesterone in patients' blood nor local hormone receptor expression in initial tracheal biopsies were examined. All patients of the present study were discussed

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Highlight box

Key findings

- Expression of female sexual hormone receptors in the fibroblasts of the trachea is a persistent finding in idiopathic tracheal stenosis.

What is known and what is new?

- Idiopathic stenosis in the cricotracheal section is a rare condition and occurs almost exclusively in females. An influence of the female sexual hormones estrogen and progesterone has been assumed previously.
- Our results confirm that the local expression of female sexual hormone receptors occurs only in idiopathic but not in posttraumatic tracheal stenosis and may therefore play a role in the genesis of this rare disease.

What is the implication, and what should change now?

- The effect of hormone intake in the genesis or prevention of this rare disease should be further investigated.

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interdisciplinary. There was a consent on primary surgery in most cases due to good surgical long-term results and missing good endoscopic or interventional options. Especially in the PTTS group, we mostly had an additional instability of the tracheal wall with no good interventional options.

Patients received resection of the stenotic tracheal segment either as tracheal resection or cricotracheal resection with primary end-to-end anastomosis using PDS (polydioxanone suture) 4/0 running suture of the posterior wall and PDS 3/0 interrupted sutures of the cartilaginous ring. Cricotracheal resections were performed in cooperation with the Department of Ear, Nose and Throat Surgery. Standardized postoperative procedure contained immediate extubation. Patients were routinely treated in the intensive care unit (ICU) for at least 1 day. Postoperative treatment consisted of regular inhalation therapy, pain killers and physiotherapy. Vocal cord function was postoperatively controlled by laryngoscopy. Respiratory and swallowing function was evaluated clinically.

Histopathological/immunohistochemical analysis

All tissue specimens were analyzed by standardized hematoxylin/eosin (HE) staining in formalin fixed sections. In addition, immunohistochemical staining using antibodies against PR (Progesterone Receptor, Clone PgR636, Mouse; Dako/Agilent) and ER (Estrogen Receptor alpha, Clone EP1, Rabbit; Dako/Agilent) was performed. All samples were stored in a tissue bank. For all tissue samples initially not analyzed by immunohistochemistry (IHC), IHC with ER and PR antibodies was performed later. A positive reaction was defined as at least weak nuclear staining specific to fibroblast nuclei, analogous to the IRS (immunoreactive score) as defined by Remmele (13).

Statistical analysis

Analysis of the whole cohort as well as comparative analysis between patients with ITS and PTTS were performed.

Statistical analysis was performed using IBM SPSS Statistics software, version 20 (SPSS Inc., Chicago, IL, USA). Data are described by means ± standard deviation or, where appropriate, by median values and ranges. Explorative group comparisons were conducted using non-parametric approaches i.e., Mann-Whitney U test, as indicated by the number of groups to be compared. All statistical tests were conducted two-sided, and a P value <0.05 was considered

to indicate statistical power. Patients lost to follow up were excluded from long-term analyses.

Ethical aspects

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics board of the Klinikum Nuremberg (IRB No. FMS_W_038.23-I-1) and informed consent was taken from all the patients.

Results

Patients' characteristics

Between 2008 and 2019, n=27 patients with a median age of 64 years (range, 16–83 years) underwent a tracheal or cricotracheal resection for nonmalignant stenosis. Cohort consists of n=6 male patients (22.2%) and n=21 female patients (77.8%). Etiology of tracheal stenosis was idiopathic in n=11 patients (40.7%) and posttraumatic in n=16 patients (59.3%) (n=7 after dilatative tracheotomy, n=8 after surgical tracheotomy, n=1 after traumatic intubation).

While posttraumatic tracheal stenoses occurred in males (n=6) as well as in females (n=10), none of the idiopathic stenoses patients were males. Consequently, there was a significant difference of gender distribution (P=0.027) and age distribution (P=0.034) between the group of ITS and PTTS (*Table 1*).

Overall, 92.6% of patients presented with comorbidities. Comparing comorbidities in the ITS and PTTS group, a higher incidence of GERD as well as goiter in the ITS group compared to the PTTS group was seen. On the other hand, arterial hypertension, diabetes mellitus, COPD and cardiovascular disease was more often in the PTTS group. Patients in the PTTS group showed significantly more often a history of smoking (P=0.016). However, none of the patients were an active smoker at the time of admission to our hospital and none of the patients abused alcohol. Only two patients showed autoimmune disease: 1 patient with autoimmune thyroiditis and 1 patient with Churg-Strauss syndrome. Analysis of ANA and ANCA was only performed in 3 patients not allowing any substantial conclusion (*Table 1*). Preceding history of oral intake of hormone compounds was notified in 11/27 (40.7%) patients: 7/11 (63.6%) in the ITS group (contraception and hormone substitution) and 4/16 (25%) in the PTTS group (only contraception). However, only one patient was taking

Table 1 Patients' characteristics of the whole cohort and both subgroups

Patients' characteristics	Whole cohort (n=27)	ITS (n=11)	Post-tracheotomy/PTTS (n=16)	P value
Gender				0.027
Female	21	11	10	
Male	6	0	6	
Age (years), median [range]	64 [16–83]	52 [24–73]	65 [16–83]	0.034
History of oral contraception/hormonal substitution				Not specified
Oral contraception	9	5	4	
Hormone substitution	2	2	0	
None	12	3	9	
Information not available	4	1	3	
Comorbidities	25 (92.6%)	10 (90.9%)	15 (93.8%)	0.658
Gastro-esophageal reflux disease	8 (29.6%)	5 (45.5%)	3 (18.8%)	0.144
Goiter of the thyroid gland	7 (25.9%)	5 (45.5%)	2 (12.5%)	0.071
Autoimmune thyroiditis	1 (3.7%)	0	1 (6.3%)	0.593
Churg-Strauss syndrome	1 (3.7%)	0	1 (6.3%)	0.593
Arterial hypertension	14 (51.8%)	1 (9.1%)	13 (81.3%)	<0.001
Diabetes mellitus	8 (29.6%)	1 (9.1%)	7 (43.7%)	0.062
Asthma	1 (3.7%)	0	1 (6.3%)	0.407
COPD	3 (11.1%)	0	3 (18.8%)	0.191
Hypercholesterinemia	4 (14.8%)	2 (18.2%)	2 (12.5%)	0.545
Cardiovascular disease	3 (11.1%)	0	3 (18.8%)	0.191
Obstructive sleep apnea	1 (3.7%)	0	1 (6.3%)	0.593
Obesity	1 (3.7%)	0	1 (6.3%)	0.593
Ex-smoker	10 (37.0%)	1 (9.1%)	9 (56.3%)	0.016
Alcohol	0	–	–	–
Preceding intervention of stenosis	9 (33.3%)	3 (27.3%)	6 (37.5%)	0.58

COPD, chronic obstructive pulmonary disease; ITS, idiopathic tracheal stenosis; PTTS, postintubation tracheal stenosis.

contraception and two patients received hormone substitution at the time of surgery. In the control group, 4/16 patients (25%) had a longer preceding history of oral contraceptives, but only one patient had reported a recent intake that stopped one year before surgery (*Table 1*).

Tracheal stenosis and surgical procedure

All patients were diagnosed by laryngoscopy and tracheobronchoscopy. Length of tracheal stenosis was described as well as remaining lumen of the trachea.

According to the Myer-Cotton classification of tracheal stenoses n=4 patients presented with grade I, n=13 patients with grad II and n=6 patients with grade III. There was no significant difference between both groups. Due to missing data Myer-Cotton classification was not possible in n=4 patients. Median length of tracheal stenosis was 2 cm (range, 1–2.5) with distance to vocal cords of median 1 cm (range, 1–4) also with no significant difference between the two groups. Neither the diameter of the normal trachea (median 15 *vs.* 17 mm) nor the remaining diameter in the stenosis (median 5.2 *vs.* 5.5 mm) differed significantly.

Table 2 Surgical procedures

Surgical procedures	Whole cohort (n=27)	ITS (n=11)	PTTS (n=16)	P value
Cricotracheal resection with laryngotracheal end-to-end anastomosis	11 (40.7)	9 (81.8)	2 (12.5)	<0.001
Tracheal resection with cricotracheal anastomosis or tracheotracheal anastomosis	16 (59.3)	2 (18.2)	14 (87.5)	<0.001
Simultaneous thyroidectomy/hemithyroidectomy	5 (18.5)	5 (45.5)	0	0.012

Data are shown as n (%). ITS, idiopathic tracheal stenosis; PTTS, postintubation tracheal stenosis.

Table 3 Expression of hormone receptors on fibroblasts in tracheal specimens

Immunohistochemistry	Whole cohort (n=27)	ITS (n=11)	PTTS (n=16)	P value
Gender				0.027
Female	21	11	10	
Male	6	0	6	
Progesterone receptors	11 (40.7%)	8 (72.7%)	3 (18.8%)	0.008
Female	10	8	2	
Male	1	0	1	
Estrogen receptors	17 (63.0%)	11 (100.0%)	6 (37.5%)	<0.001
Female	16	11	5	
Male	1	0	1	

ITS, idiopathic tracheal stenosis; PTTS, postintubation tracheal stenosis.

Stenoses in the ITS group tend to be slightly shorter and located closer to the vocal cords, but without statistical significance (Table S1).

In the whole cohort, 9 patients (33.3%) had a history of preceding interventional treatment of tracheal stenosis including tracheal stenting, laser ablation and dilatation of the stenosis. Preceding interventional treatment of tracheal stenosis was slightly more often in the PTTS group (37.5%) than in the ITS group (27.3%), but without statistical significance (P=0.58) (Table 1).

According to localization of the tracheal stenosis, patients received either segmental tracheal resection with end-to-end anastomosis (n=16) or cricotracheal resection with laryngo-tracheal end-to-end anastomosis (n=11). In 7 patients simultaneous (hemi)thyreoidectomy due to goiter was performed. Surgical procedures differed significantly between both groups (P<0.001). In the ITS group, 9/11 (81.8%) patients received cricotracheal resection while only 2/16 patient (12.5%) of the PTTS group were treated by cricotracheal resection due to the localization of the stenosis (Table 2).

Histopathology/immunohistochemistry

Malignant processes could be excluded in all patients. Histological analysis showed augmented number of fibroblasts in HE staining in 2 cases (7.4%). IHC staining revealed 11 patients (40.7%) expressing PRs and 17 patients (63%) with ERs on fibroblasts in the scar tissue. Corresponding chondromalacia was seen in n=2 patients of the PTTS group. Comparing IHC of the ITS and PTTS specimens showed significant differences between both groups: ITS specimens showed a significantly more frequent expression of PRs (72.7%) compared to the PTTS group (18.8%) (P=0.008) (Table 3, Figure 1A,1B). Moreover, ERs were expressed in 100% of ITS and only 37.5% cases in the PTTS group (P<0.001) (Table 3, Figure 2A,2B). Indeed, one male patient with PTTS expressed estrogen and PRs (Table 3).

Postoperative clinical course

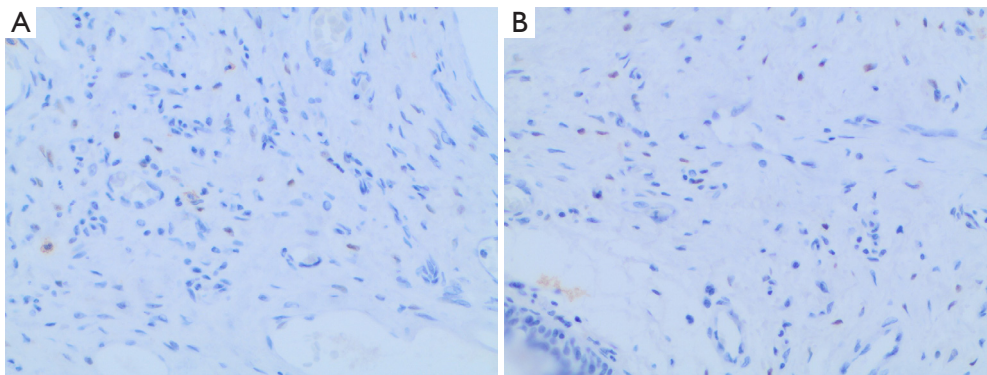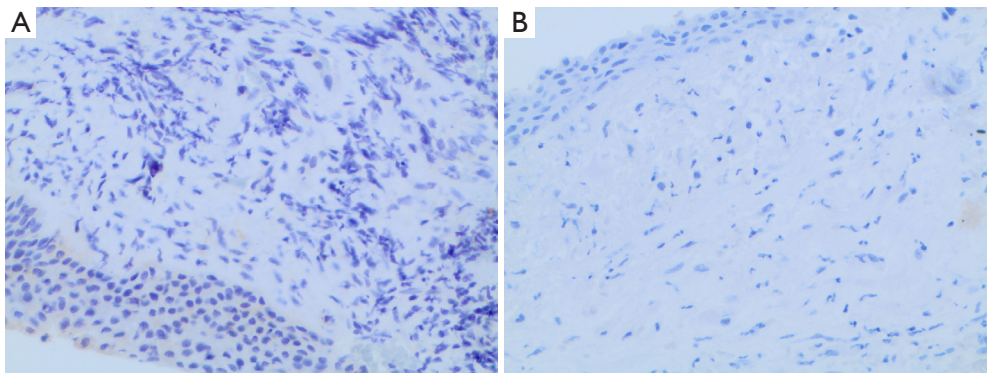Early extubation was performed in all patients. One patient

Figure 1 IHC of tracheal specimens using antibodies against progesterone receptors. (A) Formalin embed sections using IHC with antibodies against progesterone receptors on fibroblasts in tracheal specimens in the ITS group. Magnification 200×. (B) Formalin embed sections using IHC with antibodies against progesterone receptors on fibroblasts in tracheal specimens in the PTTS group. Magnification 200×. IHC, immunohistochemistry; ITS, idiopathic tracheal stenosis; PTTS, posttraumatic tracheal stenosis.

Figure 2 IHC of tracheal specimens using antibodies against estrogen receptors. (A) Formalin embed sections using IHC with antibodies against estrogen receptors on fibroblasts in tracheal specimens in the ITS group. Magnification 200×. (B) Formalin embed sections using IHC with antibodies against estrogen receptors on fibroblasts in tracheal specimens in the PTTS group. Magnification 200×. IHC, immunohistochemistry; ITS, idiopathic tracheal stenosis; PTTS, posttraumatic tracheal stenosis.

needed to be reintubated for pneumonia resulting in a median duration of intubation of 0 day (range, 0–6). All patients were discharged from the ICU after a median of 1 day (range, 1–37) and left the hospital after median 7 days (range, 3–67).

Postoperative complications occurred in n=8 patients (29.6%). In detail, 3 patients showed postoperative temporary stridor, 1 patient with hoarseness, 2 patients showed disturbance of wound healing, one patient developed postoperative pneumonia and 1 patient suffered from non-ST-elevation myocardial infarction (NSTEMI) receiving coronary angioplasty and stenting. None of the patients needed reoperation. None of the patients died. Swallowing function was sufficient in all patients. There was

no statistically significant difference regarding duration of postoperative intubation days, ICU or hospital stay between both groups. Postoperative morbidity was higher in the ITS group with 2 cases of temporary affection of the recurrent laryngeal nerve, but without statistical significance. None of the patients died and there was no need for surgical revision (*Table 4*).

Follow up and long-term results

Mean follow up of patients was 14 months with a last follow up end of 2021. n=6 patients could not be contacted for the last follow up (1 in the ITS, 5 in the PTTS). From the 21 patients, contacted for the last follow up, n=3 patients were

Table 4 Postoperative outcome

Postoperative parameters	Whole cohort (n=27)	ITS (n=11)	PTTS (n=16)	P value
Duration of intubation (days), median [range]	0 [0–6]	–	–	0.942
ICU stay (days), median [range]	1 [1–31]	–	–	0.942
Hospital stay (days), median [range]	7 [3–67]	–	–	0.865
Morbidity, n (%)	8 (29.6)	5 (45.5)	3 (18.8)	0.363
Stridor	3 (11.1)	3 (27.3)	0	
Pneumonia	1 (3.7)	0	1 (6.3)	
Hoarseness	1 (3.7)	1 (9.1)	0	
Wound infection	2 (7.4)	1 (9.1)	1 (6.3)	
NSTEMI	1 (3.7)	0	1 (6.3)	
Temporary paralysis of laryngeal recurrent nerve, n (%)	2 (7.4)	2 (18.2)	0	0.116
Mortality	0	–	–	–
Re-operation	0	–	–	–
Coronary intervention, n (%)	1 (3.7)	0	1 (6.3)	–

ICU, intensive care unit; NSTEMI, non-ST-elevation myocardial infarction; ITS, idiopathic tracheal stenosis; PTTS, postintubation tracheal stenosis.

deceased (2 in the ITS and 1 in the PTTS group) for other reasons. Of the 18 patients included in the final follow up, none of the patient had recurrence of tracheal stenosis. Only 4 patients with underlying pulmonary disease reported of slight dyspnea.

Discussion

First case of idiopathic subglottic tracheal stenosis was described by Brandenburg *et al.* in 1972. Since then, several analyses of smaller cohorts or case reports were published (14). In our data, all idiopathic tracheal stenoses were located in the upper subglottic trachea. Similarly, Mark *et al.* compared 63 cases idiopathic tracheal stenoses, receiving surgery between 1988 and 2007 in the Massachusettes General Hospital, with 34 patients resected for chondromalacia-related tracheal stenosis. All cases with ITS were female patients with the main clinical symptom of dyspnea of at least 2 years. Idiopathic tracheal stenoses were localized in the upper trachea and subglottic region. One third of patients had history of gastroesophageal reflux (15). On the contrary, Gnagi *et al.* reported only 2% of acid gastroesophageal reflux in a group of 132 ITS compared to 32% in 28 patients with acquired tracheal stenosis (16). In our analysis, gastroesophageal reflux was significantly more

often in the ITS group compared to the PTTS group.

Idiopathic tracheal stenoses are mostly related to fibrosis based on hyperactive fibroblasts. Expression of PR and ER suggests a possible activation of fibroblasts by those hormones. Expression of female sexual hormone receptors in fibroblasts of the trachea in patients with ITS is persistently described in the literature (10,11). Comparison of hormone receptor status as well as gender distribution in patients with idiopathic and non-ITS shows significant differences; even though the numbers of reported cases are small and most data is based on retrospective analyses. Wang *et al.* analyzed 263 patients with ITS. All of them were female except two patients. Hormone receptor status was only performed in 75 patients. Fifty-two showed PR and ER, 8 only a single hormone receptor and 15 patients had no hormone receptors (17). Similar to the literature, our data show that all idiopathic tracheal stenoses occurred in female patients with a strong expression of ER and PR on fibroblasts. Patients age was significant lower in the ITS group with a median age of 52 years compared to the PTTS group with a median age of 65 years. This might be relevant regarding patients' hormonal state. The role of estrogen or progesterone based oral contraception is not clear. However, anti-hormonal treatment in established stenosis might be too late. In our analysis, 63.6% of patients in the ITS group

had a preceding history of intake of hormone compounds. However, only one patient was taking contraception and two patients received hormone substitution at the time of surgery. In the control group, 4/16 patients (25%) had a longer preceding history of oral contraceptives, but only one patient had reported a recent intake that stopped 1 year before surgery. It is noteworthy that none of the patients with a history of hormone compounds in the PTTS group showed expression of ER or PR in the trachea.

In an analysis of 42 patients with idiopathic progressive subglottic stenosis by Fiz *et al.*, the median age of the cohort was similar to our data at 52.4 years old. Authors analyzed expression of alpha-estrogen receptors (alpha-ERs), beta-estrogen receptors (beta-ERs) as well progesterone receptors (PRs) in idiopathic tracheal stenoses. They showed overexpression of alpha-ER and PR, but no expression of beta-ER (11). Data were recently confirmed in a short analysis by Damrose *et al.* (10). In addition to their previous publication Fiz *et al.* analyzed the expression pattern of ER and PR in 37 (20 female, 17 male) non-idiopathic stenoses. Consistent with our findings they describe a significant over-expression of ER and PR in idiopathic in comparison to non-idiopathic stenoses. Interestingly, they found no difference in the ER expression between the female idiopathic and the subgroup of female non-idiopathic cases. On the contrary all of our ITS cases showed the ER expression but just 50% of the female PTTS patients (18).

The association of ITS and female sexual hormone receptors was initially described by case reports (12). Currently, Tapias *et al.* described the onset and/or exacerbation of ITS during pregnancy in 15 patients. In comparison to their non-pregnancy associated cases (n=248) the expression of ERs tend to be more frequent in the pregnancy associated group (100% *vs.* 75%) without statistical significance while the PR expression was exactly the same (71.4% *vs.* 72.1%) (19).

Other authors suspect genetic predisposition for idiopathic subglottic tracheal stenosis and reported a case of occurrence of idiopathic subglottic tracheal stenosis in twin sisters (20) or sisters (21) suggesting genetic predisposition of this disease.

Gelbard *et al.* analyzed the molecular pathogenesis of the fibrosing phenotype of idiopathic subglottic tracheal stenosis (ISGS) in 20 patients (with 20 healthy control specimens). ISGS specimens showed significant activation of the canonical Il-23/IL-17A pathway in the mucosa and the delta-gamma T cells as cellular source of IL-17A. In conclusion, they suggest an aberrant mucosal immune activation as part of the genesis of ISGS (22). A recent analysis published by Hillel *et al.* identified a specific microbiota of Moraxella (Prevotella and Streptococcus) that occurs significantly more often in patients with ITS compared to control group (23). A possible effect of a locally altered microbiome and a successful therapy of a idiopathic stenosis with macrolides in an 8-year-old child was reported by Tebbe *et al.* (24). Those might be additional factors favorizing the development of "idiopathic" tracheal stenosis. None of those factors were analyzed in our cohort.

Conclusions

In conclusion, different to PTTS, ITS showed significantly higher occurrence of ER and PR in fibroblasts. This supports the hypothesis of the female sexual hormone receptor-related genesis of ITS because all patients in the ITS group were female. Surgery provided good results with a favorable long-term outcome without recurrence of stenosis. Despite, the limitations of the current trial as retrospective study design and small number of patients, the findings are clear and convincing. Further investigation is needed with a special focus on hormones in the prevention of this rare disease.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1687/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1687/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1687/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics board of the Klinikum Nuremberg (IRB No. FMS_W_038.23-I-1) and informed consent was taken from all the patients.

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