Long-term histopathological changes of the nasal mucosa after total laryngectomy: a prospective cohort study*

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Abstract

Background: Changes in the nasal function following total laryngectomy resulted in histopathological alterations of the nasal mucosa. We aimed to evaluate the long-term histopathological changes and the mucociliary clearance (MCC) of the nasal mucosa after total laryngectomy.

Methods: We performed a histological examination of inferior turbinate biopsy, and saccharine test to assess the MCC time for patients who were candidates for total laryngectomy before the procedure, 6-12 months after surgery, and at least two years postoperatively.

Results: Seventy-five patients scheduled for total laryngectomy were initially enrolled in our study. We excluded patients who received postoperative radiotherapy or were lost during the follow-up period. Eventually, 63 and 54 patients were available for assessment 6-12 months after surgery and at least two years postoperatively, respectively. Except for ciliary and goblet cell destruction, which were significantly reduced 6-12 months postoperatively, there were no statistically significant differences in the histopathological findings of the nasal mucosa before surgery and 6-12 months postoperatively. After two years, the histopathological alterations of the nasal mucosa were statistically more evident than those before surgery and 6-12 months postoperatively; the most common histopathological findings were mononuclear cell infiltration and stromal fibrosis. The mean MCC time preoperatively was 12.56 minutes that statistically significantly decreased to 11.81 minutes 6-12 months after surgery; then, it significantly increased to 20.98 minutes at least two years postoperatively.

Conclusions: After total laryngectomy, the nasal mucosa showed histopathological alterations and early enhancement of the MCC, which was later impaired due to nasal mucosal atrophy and the saprophytic infection.

Key words: biopsy, histology, mucociliary clearance, nasal mucosa, laryngectomy

Introduction

Total laryngectomy results in interruption of the airway's continuity and complete respiratory dependence on a permanent tracheostomy [(1)]. Functional changes are influenced by structural alterations and the other way around. Following total laryngectomy, the upper airway cannot perform its physiological functions (e.g., warming, filtering, and moistening of the inspired air) because of the separation of the upper and the lower airways with associated changes to the nasal mucosa [(2, 3)].

After total laryngectomy, the nasal mucosa undergoes histopathological alterations, becoming thinner and changing color over time due to the absence of airflow stimulus through the nose [(4-6)]. Other changes have been observed, including the impaired sense of smell and taste, reduced nasal blood flow, and changes in the mucociliary clearance (MCC) [(4,7-11)].

Few studies evaluated the histopathological changes of the nasal mucosa and the nasal MCC after the total laryngectomy; most were cross-sectional studies with a control group of healthy individuals, affecting the results' validity [(3, 11, 12)]. They did not consider the individual variations regarding the nasal histology

Table 1. Demographic data and smoking habits of our patients.

Age (years) (mean ±SD)		57.2 ± 12.9 (Ranged from 47 - 71 years)
Sex	Males	72/75 (96%)
	Females	3/75 (4%)
Smoking Status	Number of Cigarettes smokers	75/75(100%)
	Number of cigarettes smoked per day (mean ±SD)	26 ± 7.59 (Ranged from 15–40 cigarettes/day)
	Duration of smoking (years) (mean ±SD)	16.80 ± 6.20 (Ranged from 7–35 years)

and the nasal MCC since most patients with total laryngectomy were elderly and cigarette smokers. The purpose of our study was to look at the long-term histopathological alterations of the nasal mucosa and the changes of the nasal MCC in patients with total laryngectomy.

Materials and methods

Study design, setting, and participants

We conducted this observational prospective cohort study between March 2014 and June 2020. Our study included seventy-five patients who agreed to have a total laryngectomy for advanced laryngeal cancer in (Blinded for review) at the Department of Otorhinolaryngology, Tanta University Hospital, Egypt.

Data measurement

1. We have taken inferior turbinate biopsy for histological examination by light and electron microscopes in patients before the total laryngectomy, 6-12 months following surgery, and at least two years postoperatively. We compared their findings with the histological examination of the nasal mucosa of the inferior turbinate in three healthy volunteers (control specimens), nonsmokers aged less than forty years, with no history of chronic sinonasal mucosal disease.
2. We assessed the nasal MCC time by the Saccharine test in the wider nasal cavity in patients before the total laryngectomy, 6-12 months after surgery, and at least two years postoperatively. We compared their results with the nasal MCC time in thirty healthy control volunteers who were nonsmokers and had no history of chronic sinonasal mucosal disease.

The histological examination

We used thru-cutting forceps to take a biopsy one cm behind the anterior end of the inferior turbinate in patients before the total laryngectomy, 6-12 months following surgery, a minimum of two years after surgery, and from the subjects in the control group under local anesthesia with a submucosal infiltration of 2 percent lignocaine/ 1:200 000 adrenaline. We fixed the specimens in 2.5 percent phosphate-buffered glutaraldehyde and washed them three times with phosphate-buffered saline (10 minutes each) before being dehydrated with a rising titer of ethyl alcohol (30%, 50%, 70%, 90%, and 100%), then infiltrated with Araldite. We placed each specimen in the tip of a capsule with its label.

The capsules were polymerized in an oven at 35˚C for 24 hours, at 45˚C, and finally at 60˚C for three days. The polymerized blocks were allowed to cool before being used. They were ready for sectioning when they became very hard. For the preparation of the semithin sections, we trimmed the blocks using a dissecting microscope. Sections were cut by LEICA ultramicrotome (Germany) at 850 nm "semithin sections" and were mounted on glass slides, then stained with toluidine blue (1%). We used a light microscope to examine the inferior turbinate's semithin sections.

For ultrastructural analysis under transmission electron microscopy, we retrimmed the block face. Sections of 75 nm in thickness were cut by LEICA ultramicrotome. We picked up the sections on 200 mesh uncoated copper grids. The grids were double-stained with uranyl acetate and lead citrate. Finally, the specimens were examined and photographed using (JEOL-JEM-100 SX electron microscope, Japan) with AMT camera at The Electron Microscopic Unit (Faculty of Medicine, Tanta University, Egypt).

The nasal mucociliary clearance time by saccharin test

We have conducted the saccharine test with the participants seated and their heads held upright. We told them to clean the nasal secretions before inserting a saccharin tablet (1x1x1 mm) into the wider side of the nasal cavities, one cm posterior to the anterior end of the medial surface of the inferior turbinate. We asked them not to sniff or flex their heads during the test. We instructed the participants to swallow once every thirty seconds and tell us as soon as they tasted the saccharin. We measured the time to the initial perception of the sweet taste in minutes (the MCC time).

Sample size calculation and statistical method

We utilized the Epi-info software created by the world health organization and center for disease control and prevention (Atlanta, GA, USA) to calculate the sample size. The power analysis explained that recruiting 50 participants would give 80 % power to detect changes in the mucociliary clearance time and the his-

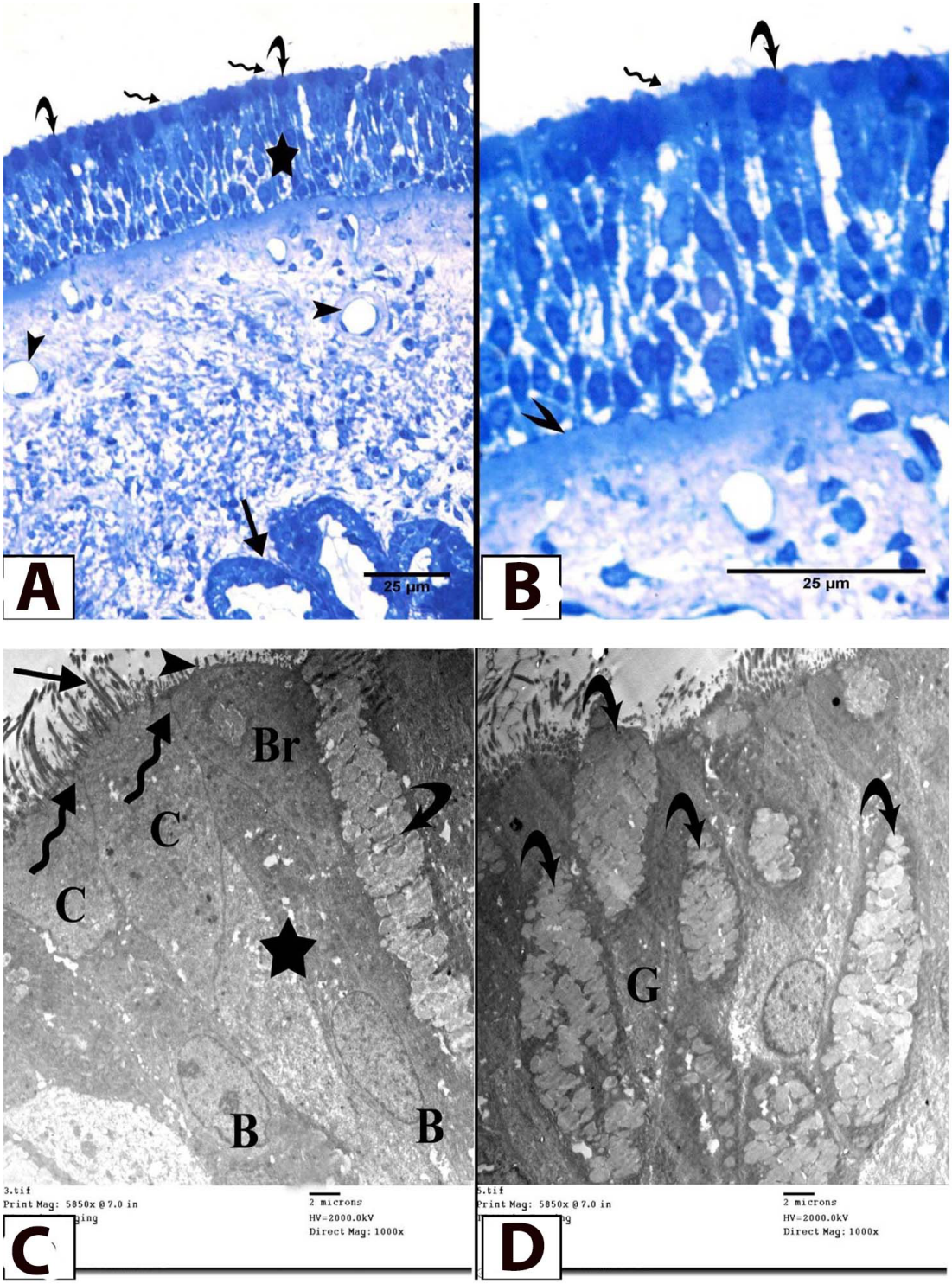

Figure 1. A, B: Semithin sections of the nasal mucosa of the control specimens showing the typical histological structure of the respiratory epithelium of the nasal mucosa: A- Normal respiratory epithelium (star) with ciliated columnar cells (zigzag arrows) & goblet cells (curved arrows). Underlying submucosa showing blood vessels (arrow heads) and glands (straight arrow) (Toluidine blue, Mic. Mag. ×400), B- Higher magnification of (A) photograph showing ciliated columnar cells (zigzag arrow) & goblet cells (curved arrow). Notice the underlying basement membrane (arrowhead) (Toluidine blue, Mic. Mag. ×1000). C, D: An electron micrograph of the nasal mucosa of the control specimens showing the typical histological structure of the respiratory epithelium of the nasal mucosa: C- Normal respiratory epithelium (star) formed of columnar cells (C) with their cilia (straight arrow), goblet cell with its mucus granules (curved arrow), basal cells (B), brush cells (Br) with apical microvilli (arrowhead). Notice normal junctional complex between the cells (zigzag arrows) (Mic. Mag. ×1000). D- Multiple Goblet cells (G) with their mucus granules (curved arrows) (Mic. Mag. ×1000).

Table 2. The histopathological alterations of the nasal mucosa before total laryngectomy, 6-12 months after surgery, and at least two-years postoperatively.

	Before Total laryngectomy		Six-twelve months after total laryngectomy		At least two years after total laryngectomy		p-value 1	p-value 2	p-value 3
	Patients (N = 75)		Patients (N = 63)		Patients (N = 54)				
	N	%	N	%	N	%			
Focal atrophy of the nasal mucosa	12	16	9	14.3	27	50	0.780	0.001*	0.001*
Total atrophy of the nasal mucosa	2	2.7	3	4.8	10	18.5	0.512	0.002*	0.018*
Widened intercellular spaces and loss of the junctional complexes	12	16	11	17.5	23	42.6	0.817	0.001*	0.003*
Thickening of basement membrane	14	18.7	13	20.6	35	64.8	0.772	0.001*	0.001*
Squamous metaplasia	15	20	9	14.3	15	27.8	0.378	0.018*	0.004*
Destruction of the goblet cells	33	44	17	27	37	68.5	0.038*	0.006*	0.001*
Destruction of the cilia	31	41.3	16	25.4	33	61.1	0.049*	0.027*	0.005*
Fibrosis of the nasal stroma	29	38.7	26	41.3	41	75.9	0.756	0.001*	0.001*
Mitochondrial swelling and degeneration	9	12	8	12.7	15	27.8	0.901	0.023*	0.041*
Neo-angiogenesis	11	14.7	9	14.3	21	38.9	0.950	0.002*	0.002*
Destruction of the sub-epithelial glands	4	5.3	3	4.8	24	44.4	0.879	0.001*	0.001*
Mononuclear cell infiltration as neutrophil, mast cells, plasma cells, and fibroblast	21	28	16	25.4	46	85.2	0.731	0.001*	0.001*

p-value 1, p-value 2, and p-value 3: Results of the p-value comparing the differences in the histopathological findings of the nasal mucosa between the different follow-up periods, p-value 1: Before total laryngectomy and 6-12 months postoperatively, p-value 2: Before total laryngectomy and at least two years postoperatively, p-value 3: Six to twelve months postoperatively and at least two years postoperatively. * Statistically significant at p-value < 0.05. N: Number of patients, %: percentage

topathological alterations of the nasal mucosa in patients before the total laryngectomy, 6-12 months after surgery, and at least two years postoperatively.

We analyzed the collected data utilizing computer software (SPSS version 15; SPSS Institute, Chicago, IL). We have expressed the quantitative data as a mean ± standard deviation (SD). We used a one-way analysis of variance (ANOVA) for comparison between groups, followed by a Post Hoc test for comparison between different variables (continuous variable). We used Chi-square (X2) test for comparison between groups for the categorical variables. Statistical significance was considered as a p-value less than 0.05.

We performed multivariate regression analysis to determine whether the age, the number of cigarettes smoked per day, and the duration of smoking were independent variables related to the histopathological alterations of the nasal mucosa and the nasal MCC time (dependent variables) in patients before total laryngectomy.

Ethical consideration

The institutional review board (IRB) of the Faculty of Medicine at Tanta University approved our study, and we received informed consent from all the participants in our study. Only members of the responsible research team have collected the patient information and reviewed it.

Results

Our study included seventy-five patients who underwent total laryngectomy with bilateral selective neck dissection. Table 1 summarizes their demographic data and smoking habits; all of them quitted smoking after surgery.

Six to twelve months after total laryngectomy, sixty-three patients were available for assessment after excluding patients

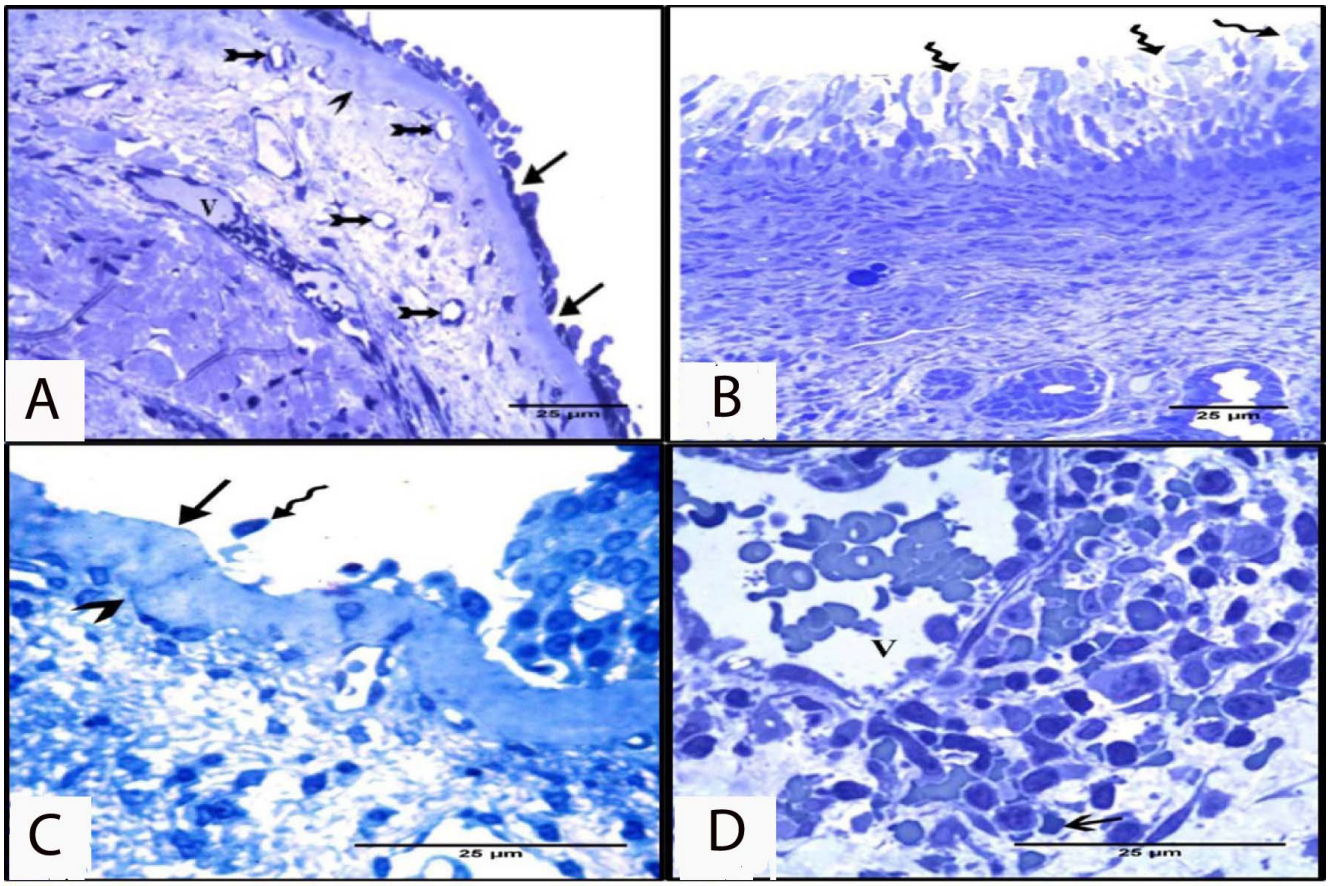

Figure 2. Semithin sections of nasal mucosa two years after total laryngectomy showing: A- Focal atrophy of the nasal mucosa (straight arrows) and neo-angiogenesis in the submucosa (bifid arrows) with dilated blood vessel (V). Notice focal basement membrane thickening (arrowhead) (Toluidine blue, Mic. Mag. ×400). B- Widening of epithelial cell intercellular spaces and separation of epithelial cells from each other (zigzag arrows) (Toluidine blue, Mic. Mag. ×400). C- Total atrophy nasal mucosa (straight arrow) with desquamated cells (zigzag arrow). Marked basement membrane thickening (arrowhead) was also noticed (Toluidine blue, Mic. Mag. ×1000). D- Submucosa with prominent mononuclear cellular infiltration (straight arrow) and dilated blood vessel (V) (Toluidine blue, Mic. Mag. ×1000).

who received adjuvant radiation or chemo-radiotherapy and patients who were lost during the follow-up period. After two years, only fifty-four patients completed our study.

The histological examination of the inferior turbinate biopsy using light and electron microscopes

We had control specimens from the inferior turbinates of three healthy volunteers, nonsmokers, with no history of chronic sinonasal disease. Their ages ranged from 23-38 years (mean, 31 ± 7.55 years). Their semithin sections and electron microscopic examination showed the typical histological structure of the respiratory epithelium of the nasal mucosa. The respiratory epithelium appeared as pseudostratified columnar ciliated epithelium. It was formed of ciliated columnar cells, goblet cells with wide apical portions contained mucus granules, brush cells with apical microvilli, and basal cells, as shown in Figure 1. The ordinary intercellular spaces and junctional complexes between the epithelial cells were preserved.

Table 2 demonstrates the results of the histological examination of the nasal biopsies that were taken from the patients before the total laryngectomy, which revealed that the most common histopathological alterations were: goblet cell destruction in 33/75 patients (44%), ciliary destruction in 31/75 patients (41.3%), fibrosis of nasal stroma in 29/75 patients (38.7%), and mononuclear cell infiltration in 21/75 patients (28%).

Multivariate regression analysis identified the age, the number of cigarettes smoked per day, and the duration of smoking as statistically significant contributors (p-value = 0.001, 0.007, and 0.013 respectively) to the histopathological changes of the nasal mucosa in patients before total laryngectomy.

There were no statistically significant differences in the histopathological findings of the nasal mucosa in patients before total laryngectomy and patients 6-12 months after surgery except for ciliary and goblet cell destruction, which were statistically

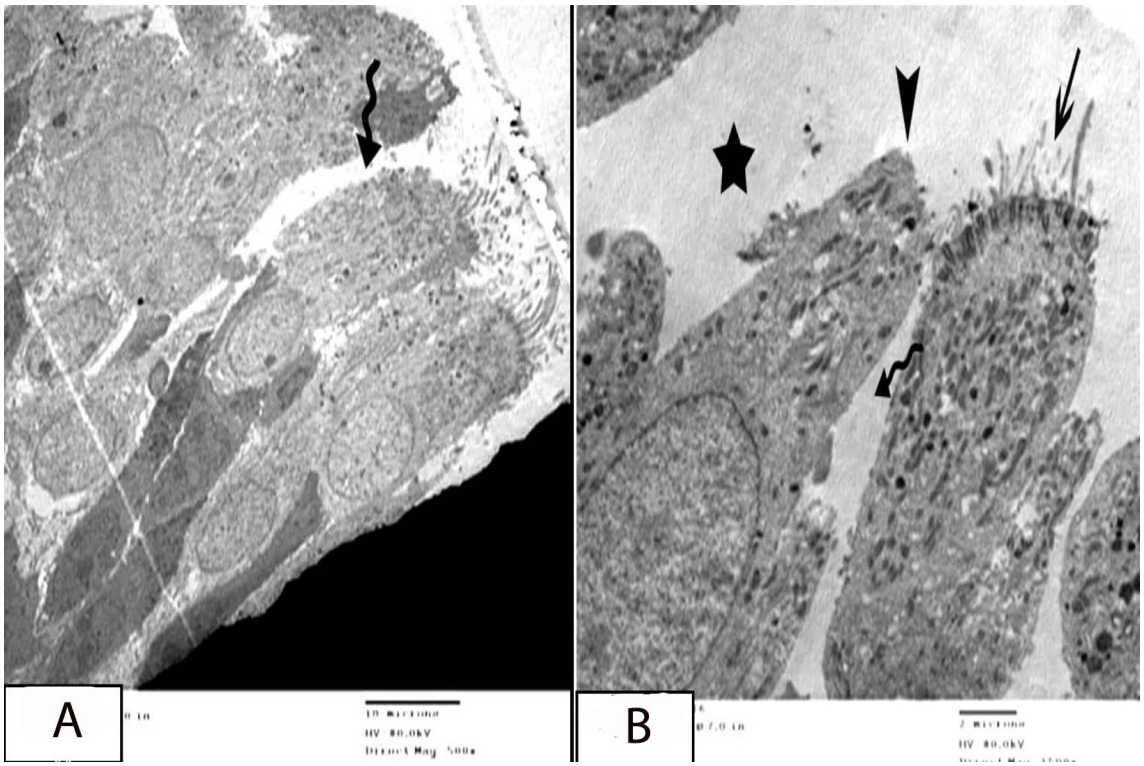

Figure 3. An electron micrograph of the nasal mucosa taken two years after total laryngectomy showing: A- Widening of intercellular space with loss of the junctional complexes (zigzag arrow) (Mic. Mag. ×500). B- Some cells showed complete loss of their cilia (arrowhead), while others showed few cilia (straight arrow). Notice widening of intercellular space (zigzag arrow) and focal loss of epithelial cells (star) (Mic. Mag. ×1500).

significantly reduced 6-12 months after total laryngectomy as demonstrated in Table 2.

The histopathological findings in patients at least two years after total laryngectomy (mean, 35.08 ± 6.07 months; ranging from 24 to 45 months) showed statistically significant differences when compared to those in patients preoperatively and patients with a follow-up period between six to twelve months after surgery, as highlighted in Table 2. The most common histopathological findings of the nasal mucosa in patients at least two years after total laryngectomy were: mononuclear cell infiltration as neutrophil, mast cells, plasma cells, and fibroblast in 46/54 patients (85.2%), fibrosis of the nasal stroma in 41/54 patients (75.9%), destruction of the goblet cells in 37/54 patients (68.5%), thickening of basement membrane in 35/54 patients (64.8%), destruction of the cilia in 33/54 patients (61.1%), and focal atrophy of the nasal mucosa in 27/54 patients (50%), as demonstrated in Figures 2 and 3.

The nasal mucociliary clearance (MCC) time

The mean nasal MCC time in patients before total laryngectomy was 12.56 ± 1.49 minutes (ranging from 10.8 – 16 minutes), which was statistically significantly shortened (p-value=0.016) six to twelve months after surgery to 11.81 ± 1.89 minutes (ranging from 8.5 to 14.7 minutes). Then it statistically significantly increased (p-value=0.001) to 20.98 ± 1.31 minutes (ranging from 17.9 to 23.1 minutes) in patients at least two years after total laryngectomy, as shown in Figure 4.

The multivariate regression analysis showed that the age, the number of cigarettes smoked per day, and the duration of smoking were statistically significant independent variables (p-value = 0.001, 0.010, and 0.021, respectively) associated with increased nasal MCC time in patients before total laryngectomy.

The control group included thirty healthy volunteers, nonsmokers, 17 males, and 13 females; their ages ranged from 30-58 years (mean, 41.5 ± 8.6 years). Their mean nasal MCC time was 11.15 ± 1.67 minutes (with a range of 7.9 to 14.2 minutes), which was statistically significantly shorter when compared to the mean nasal MCC time in patients before the total laryngectomy and patients with at least two years postoperatively. However, there was no statistically significant difference in the mean nasal MCC time between the subjects in the control group and the patients 6-12 months after total laryngectomy.

Discussion

Patients with total laryngectomy are the best models to assess the histological and physiological changes of the nasal mucosa that result from the absence of airflow through the nose. Our goal was to assess the histopathological alterations of the nasal mucosa and the changes of the nasal mucociliary clearance

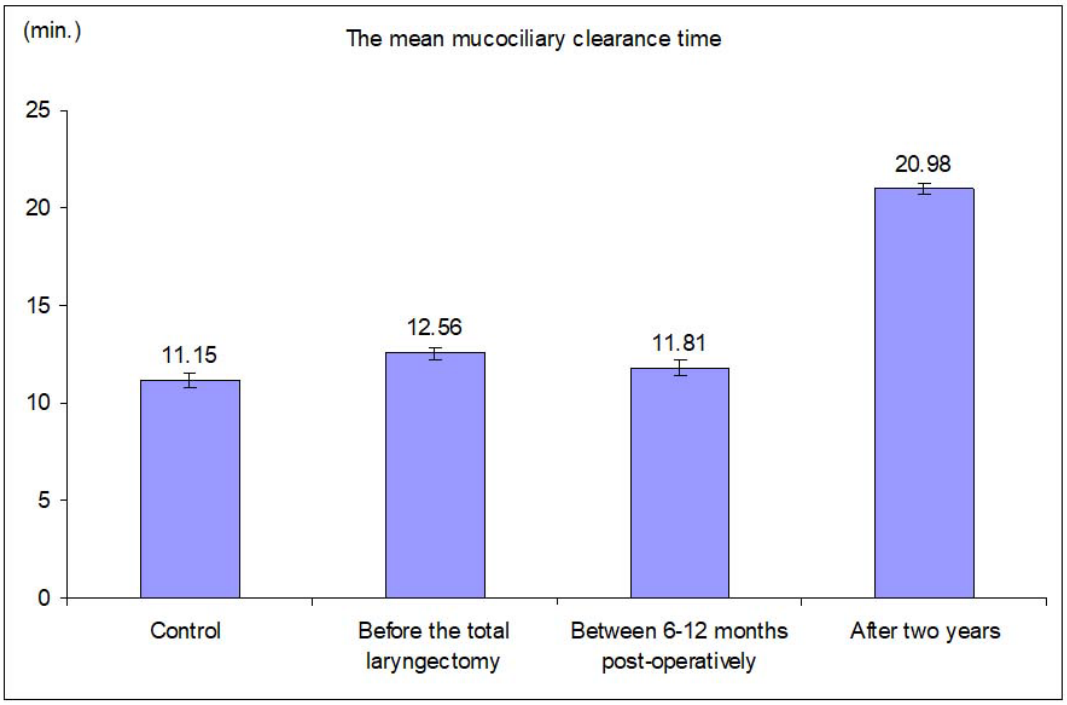

Figure 4. A bar graph illustrating the mean and the standard error "Error Bars" of the nasal MCC time in subjects of the control group, in patients before the total laryngectomy, 6-12 months postoperatively, and at least two years after surgery.

(MCC) time in patients before total laryngectomy, 6-12 months after surgery, and at least two years following surgery.

Our study revealed that the most common histopathological findings of the nasal mucosa in the patients before total laryngectomy were the destruction of goblet cells in 44% of patients, ciliary destruction in 41.3% of patients, fibrosis of the nasal mucosa in 38.7% of patients, and mononuclear cell infiltration as neutrophil, mast cells, plasma cells, and fibroblast in 28% of patients. In our study, the multivariate regression analysis showed that the age, the number of cigarettes smoked per day, and the duration of smoking were all statistically significant predictors of the histopathological changes of the nasal mucosa before total laryngectomy. So, we attributed these histopathological changes before total laryngectomy to the advanced age of our patients, and they were cigarette smokers.

Schrodter et al. [13] investigated the nasal mucosal changes related to the age and found that thin atrophic epithelium with thickening of the basement membranes was only seen in people over the age of forty. Another case series study conducted by Pagliuca et al. [14] demonstrated that cigarette smoking altered the cytology of the nasal mucosa with a significant decrease of the number of ciliated cells and impairment of ciliary motility. They claimed that these changes were not permanent and that the nasal mucosa of ex-smokers reverted to normal cytologic and functional characteristics.

Except for ciliary and goblet cell destruction, which were statistically significantly reduced in patients 6-12 months after total laryngectomy, there were no statistically significant differences in the histopathological findings of the nasal mucosa in patients before total laryngectomy and 6-12 months after surgery.

The histopathological alterations in patients at least two years after total laryngectomy showed statistically significant differences when compared to those before surgery and 6-12 months postoperatively. The most common findings were mononuclear cell infiltration in 85.2% of patients, fibrosis of the nasal stroma in 75.9% of patients, destruction of the goblet cells in 68.5% of patients, thickening of basement membrane in 64.8% of patients, and ciliary destruction in 61.1% of patients.

Several studies have investigated the relationship between airflow cessation through the nose and the associated histopathological changes [15-17]. Karaca et al. [12] studied the histopathological changes of the nasal mucosa in eleven patients who underwent total laryngectomy; they reported that the most common findings were goblet cell destruction and stromal fibrosis in 81% of the patients, followed by focal atrophy and destruction of the subepithelial glands in 45 % of patients. Other changes were noticed, including complete mucosal atrophy

with myxoid degeneration and neovascularization. According to Skoloudik et al. [11], the main nasal mucosa cytological changes after total laryngectomy were the basal cells hyperplasia and secondary bacterial infection.

Riva et al. [9] studied 25 patients who had total laryngectomy and 25 healthy controls with more than two years of follow-up. The nasal cytology showed that 20% of the laryngectomy patients had cellular metaplasia, which was not present in the control group, and that neither group had squamous cell metaplasia nor atypia. In their study, eleven patients agreed to have a biopsy from the inferior turbinate, which revealed submucosal stromal fibrosis in all of them and inflammatory infiltrate of the submucosa in one case.

Maurizi et al. [17] used electron microscopy to examine the nasal mucosa of three cases with unilateral choanal atresia. They observed superficial mucosal irregularities, basement membrane thickening, and ciliary morphological changes. Fisher et al. [18] and Cvetnic et al. [16] reported degenerative changes of the ciliated respiratory epithelium and goblet cells reduction of the nasal mucosa in patients who had a total laryngectomy.
Cagici et al. [19] observed epithelial cell detachment with a lack of goblet cells in the nasal mucosa of the patients with nasal vestibule stenosis. The superficial epithelial layer had no cilia, but some had microvilli with numerous secretory vesicles underneath. Some epithelial cells had their junctional units separated, with lipid droplets accumulation in these abnormally formed spaces.
The structural changes of the nasal mucosa following the total laryngectomy result in short- and long-term changes in the nasal MCC which can be measured by the Saccharin test with an average value of 9 to 17 minutes [20-23].

Our study demonstrated that the mean nasal MCC time in patients six to twelve months after total laryngectomy was significantly shorter than before surgery. However, after a two-year follow-up, the MCC significantly deteriorated with a mean nasal MCC time of 20.98 ± 1.31 minutes. In subjects in the control group, the mean nasal MCC time was statistically significantly shorter than in patients before total laryngectomy and patients at least two years after surgery.

According to the multivariate regression analysis, the age, the number of cigarettes smoked per day, and the smoking duration exhibited a statistically significant adverse effect on the nasal mucociliary clearance before total laryngectomy. As a result, we attributed the impairment of the nasal MCC in patients before total laryngectomy to their advanced age, and they were all cigarette smokers. Ho et al. [24] reported that individuals older than forty years had significantly longer nasal MCC times than their younger counterparts. Prasetyo et al. [25] conducted a systematic review to explore the nasal MCC in smokers; they demonstrated that fifteen out of sixteen articles showed the impairment of nasal MCC in smokers.
Maurizi et al. [26] evaluated the nasal MCC and the mucosal changes in forty patients with a total laryngectomy. They observed improvement of the nasal MCC sixty days after surgery, which deteriorated in six patients who completed a five-year follow-up period. They also showed that six months after surgery, the transitional and squamous epithelia of the anterior third of the inferior turbinate had partially transformed into a columnar ciliated type.

Kocak et al. [20] conducted a study including 23 patients who underwent total laryngectomy utilizing acoustic rhinometry before and after administration of nasal decongestant to assess the inferior turbinate mucosal contractility and saccharin test for assessment of the nasal MCC. They described that the inferior turbinate contractile capacity diminished over time in patients with a total laryngectomy. They demonstrated that the nasal MCC time did not significantly alter in the first month following surgery compared to the preoperative value; however, it significantly decreased in the sixth postoperative month. There was no statistically significant difference in the nasal MCC time between six and twelve months after surgery.

Denis et al. [23] used the saccharine test to assess the nasal MCC in 39 patients with a total laryngectomy and 36 healthy subjects. They demonstrated that the nasal MCC time in patients who underwent total laryngectomy with a follow-up period of less than 2-years duration was 8.15±2.06 minutes, which was statistically significantly shorter than in patients who had total laryngectomy with a follow-up period of more than two years (23.79 ±5.58 minutes) and the healthy subjects (14.5±3.55 minutes).

In a study including 22 patients with total laryngectomy and 24 healthy subjects, Karaoglu et al. [3] investigated the late-term effect (at least two years after surgery) of the total laryngectomy on the nasal function utilizing acoustic rhinometry, saccharine test, and smell identification test. They demonstrated that the patients with laryngectomy had more nasal passage patency (no significant difference between both groups), significantly lower olfactory scores, and longer nasal MCC time (average was 662.5 seconds for thirteen healthy subjects and 1017.14 seconds for twenty-one cases in the patient group) when compared to the healthy subjects.

Dixon et al. [21] investigated the nasal mucosal changes after total laryngectomy. They observed squamous epithelium to the ciliated columnar epithelium transformation, increased nasal MCC time, and a color change of the nasal mucosa (from pink to

light purple). Two months following total laryngectomy, Todisco et al. [27] observed enhancement of the MCC due to the hypersecretory phase.
Moore et al. [22] investigated twenty-three patients with total laryngectomy and ten patients about to have one. Scanning electron microscopy revealed that the patients with a total laryngectomy had a more densely ciliated nasal epithelium and significantly faster MCC than the preoperative controls.

Our results demonstrated a significant reduction of the ciliary destruction 6-12 after total laryngectomy, which could justify the improvement of the nasal MCC in the early postoperative period. Previous studies [11, 26, 27] revealed that the enhancement of the nasal MCC early after the total laryngectomy might result from the predominance of ciliated columnar epithelium, an increase of the endonasal humidity and temperature, absence of the nasal cycle, and reduction of the endonasal blood flow. Smoking cessation after surgery might be a confounding factor for this early improvement of the nasal MCC due to ciliary structure and function improvement, a decrease of epithelial metaplasia, and restoration of ionic transport function [28,29]. Two years after total laryngectomy, our findings demonstrated a marked nasal mucosal atrophy with ciliary destruction, which could explain why the nasal MCC deteriorated two years after total laryngectomy. Our results were consistent with those of Maurizi et al. [26], who found that deterioration of the nasal MCC five years after total laryngectomy could arise from the atrophy of the nasal mucosa, decreased endonasal humidity and temperature, and secondary saprophytic bacterial infections [26].

Most of the previous studies evaluated the histopathological alterations and the nasal MCC changes in patients with total laryngectomy compared to a healthy control group or with no comparison groups. They did not consider the variations between the individuals regarding the nasal histology and the nasal MCC, especially most of the patients with laryngectomy were elderly and cigarette smokers. Therefore, we designed a longitudinal observational cohort study to detect the histopathological alterations and the nasal MCC changes in patients before total laryngectomy, 6-12 months after surgery, and at least two years postoperatively.

Conclusion

Following total laryngectomy, functional changes of the nose may result in histopathological alterations of the nasal mucosa, including mononuclear cell infiltration, stromal fibrosis, mucosal atrophy, ciliary and goblet cells destruction, and thickening of the basement membrane. The nasal mucociliary clearance improved early after the total laryngectomy, but it deteriorated later due to decreased endonasal temperature and secondary saprophytic bacterial infections.

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None.

Authorship contribution

MOT, AEN, and MAA contributed to clinical examination, surgery. AY, HEA, MS, MME, and MOT helped with data collection, writing, and manuscript preparation.

Conflict of interest

All authors declare no conflict of interest (financial or non-financial).

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References

1. Patel VA, Pool CD, Dunklebarger M, Schaefer E, Goyal N. Sinonasal Disease in Total Laryngectomy Patients. Ann Otol Rhinol Laryngol 2019;128:811-818.
2. Ackerstaff AH, Hilgers FJ, Aaronson NK, Balm AJ. Communication, functional disorders and lifestyle changes after total laryngectomy. Clin Otolaryngol Allied Sci 1994;19:295-300.
3. Karaoglu D, Kocyigit M, Ortekin SG, Adali MK. Late-term Effects of Surgery on Nasal Functions in Patients who Underwent Total Laryngectomy Surgery. Int Arch Otorhinolaryngol 2017;21:270-275.
4. Bende M. Blood flow in human nasal mucosa after total laryngectomy. Acta Otolaryngol 1983;96:529-531.
5. Ozgursoy OB, Dursun G. Influence of long-term airflow deprivation on the dimensions of the nasal cavity: a study of laryngectomy patients using acoustic rhinometry. Ear Nose Throat J 2007;86:488, 90-92.
6. Miani C, Ortolani F, Bracale AM, Petrelli L, Staffieri A, Marchini M. Olfactory mucosa histological findings in laryngectomees. Eur Arch Otorhinolaryngol 2003;260:529-535.
7. Drake AF, Keall H, Vig PS, Krause CJ. Clinical nasal obstruction and objective respiratory mode determination. Ann Otol Rhinol Laryngol 1988;97:397-402.
8. Fisher EW, Liu M, Lund VJ. The nasal cycle after deprivation of airflow: a study of laryngectomy patients using acoustic rhinometry. Acta Otolaryngol 1994;114:443-446.
9. Riva G, Boita M, Corvino A , et al. Nasal and Tracheal Cytological Changes After Total Laryngectomy in Long-Term Survivors. Ann Otol Rhinol Laryngol 2017;126:124-131.
10. Sakakura Y, Ukai K, Majima Y, Murai S, Harada T, Miyoshi Y. Nasal mucociliary clearance under various conditions. Acta Otolaryngol 1983;96:167-173.
11. Skoloudik L, Vokurka J, Zborayova K, Celakovsky P, Kucera M, Ryska A. Cytology of the nasal mucosa after total laryngectomy. Acta Otolaryngol 2009;129:1262-1265.
12. Karaca CT, Gultekin E, Yelken MK, Igdem AA, Kulekci M. Long-term histologic changes in nasal mucosa after total laryngectomy. Int J Otolaryngol 2010;2010:137128.
13. Schrödter S, Biermann E, Halata Z. Histological evaluation of age-related changes in human respiratory mucosa of the middle turbinate. Anat embryol 2003;207:19-27.
14. Pagliuca G, Rosato C, Martellucci S, et al. Cytologic and functional alterations of nasal mucosa in smokers: temporary or permanent damage? Otolaryngol Head Neck Surg. 2015;152:740-745.
15. Jang YJ, Myong NH, Park KH, Koo TW, Kim HG. Mucociliary transport and histologic

characteristics of the mucosa of deviated nasal septum. Arch Otolaryngol Head Neck Surg 2002;128:421-424.
16. Cvetnic V, Sips D. Clinical and cytomorphological alterations of nasal mucosa in laryngectomized patients. Rhinology 1988;26:183-189.
17. Maurizi M, Ottaviani F, Paludetti G, Spreca A, Almadori G. Choanal atresia: a surface and ultrastructural study of the nasal mucous membranes. Int J Pediatr Otorhinolaryngol 1985;10:53-66.
18. Fisher EW, Lund VJ, Rutman A. The human nasal mucosa after deprivation of airflow: a study of laryngectomy patients Rhinology. 1992;30:5-10.
19. Cagici CA, Karabay G, Yilmazer C, Gencay S, Cakmak O. Electron microscopy findings in the nasal mucosa of a patient with stenosis of the nasal vestibule Int J Pediatr Otorhinolaryngol 2005;69:399-405.
20. Kocak I, Dogan R, Eren SB, Tugrul S, Ozturan O, Hafiz AM. Changes occurring in mucosal contractility of the inferior turbinate and mucociliary clearance following total laryngectomy: A prospective clinical trial. Auris nasus larynx 2018;45:332-336.
21. Dixon FW, Hoerr NL, Mc CJ. The nasal mucosa in the laryngectomized patients. Ann Otol Rhinol Laryngol 1949;58:535-547.
22. Moore-Gillon V. The nose after laryngectomy. J R Soc of Med 1985;78:435-439.
23. Deniz M, Uslu C, Ogredik EA, Akduman D, Gursan SO. Nasal mucociliary clearance in total laryngectomized patients. Eur Arch Otorhinolaryngol 2006;263:1099-1104.
24. Ho JC, Chan KN, Hu WH, et al. The effect of aging on nasal mucociliary clearance, beat frequency, and ultrastructure of respiratory cilia. Am J Respir Crit Care Med 2001;163:983-988.
25. Prasetyo A, Sadhana U, Budiman J. Nasal Mucociliary Clearance in Smokers: A Systematic Review. Int Arch Otorhinolaryngol 2021;25:160-169.
26. Maurizi M, Paludetti G, Almadori G, Ottaviani F, Todisco T. Mucociliary clearance and mucosal surface characteristics before and after total laryngectomy. Acta Otolaryngol 1986;102:136-145.
27. Todisco T, Maurizi M, Paludetti G, Dottorini M, Merante F. Laryngeal cancer: long-term follow-up of respiratory functions after laryngectomy. Respiration 1984;45:303-315.
28. Utiyama DM, Yoshida CT, Goto DM, et al. The effects of smoking and smoking cessation on nasal mucociliary clearance, mucus properties and inflammation. Clinics (Sao Paulo, Brazil) 2016;71:344-350.
29. Ramos EM, De Toledo AC, Xavier RF, et al. Reversibility of impaired nasal mucociliary clearance in smokers following a smoking cessation programme. Respirology 2011;16:849-855.

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