The Histopathology of the Hypertrophic Inferior Turbinate

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**Objective:** To analyze the quantitative and qualitative characteristics of the hypertrophic inferior turbinate (IT).

**Design:** A prospective, nonrandomized, controlled, morphometric study.

**Setting:** University-affiliated hospital.

**Subjects:** Seventeen patients with refractory IT hypertrophy and 12 with normal ITs.

**Interventions:** Twenty ITs were removed from patients with refractory IT hypertrophy and 14 from patients with normal ITs.

**Main Outcome Measures:** The soft tissue and bony elements and the relative proportions of the soft tissue constituents of the hypertrophic and normal ITs were measured and compared. The Bonferroni correction was used to adjust for multiple comparisons. Qualitative assessment was performed to assess possible pathologic changes in all IT tissues.

**Results:** The hypertrophic ITs were significantly wider. The medial mucosal layer, which thickened from a mean ± SD of 1.39 ± 0.28 mm to 2.53 ± 0.56 mm (P < .001), made the greatest contribution to the total increase in the width of the IT (64.4%). The enlargement in width of the lateral mucosal layer from 0.91 ± 0.26 mm to 1.26 ± 0.31 mm was of borderline statistical significance. The portion of the medial, lateral, and inferior layers of the lamina propria that houses inflammatory cells enlarged significantly in patients with IT hypertrophy compared with healthy control subjects. The relative proportion of the connective tissue, submucosal glands, and arteries remained unchanged, whereas that of venous sinusoids increased significantly in all aspects of the hypertrophic mucosa. Fibrosis, inflammation, and engorged venous sinusoids were noted in hypertrophic ITs, yet there was no evidence of tissue destruction.

**Conclusion:** Understanding the histopathology of the hypertrophic IT is imperative for the development and management of IT reduction surgery.


**METHODS**

Twenty hypertrophic ITs, 3 pairs and 14 single samples, were obtained from 15 men and 2 women ranging in age from 18 to 61 years (mean ± SD age, 29.2 ± 11.6 years). All patients had clinically prolonged nasal obstruction caused by marked bilateral ITH and failed to respond to prolonged perceived nasal obstruction resulting from inferior turbinate hypertrophy (ITH) is a common complaint encountered in the practice of rhinology. Several causes may induce significant hypertrophic mucosal changes of the inferior turbinate (IT), including perennial allergic rhinitis and nonallergic (vasomotor) rhinitis. Our patients are usually offered conservative therapy with antihistamines, systemic decongestants, topical nasal steroid sprays, and mast cell stabilizers. When these means do not provide adequate relief for the patient, surgery is suggested. Over the years, a variety of reduction techniques have been introduced with the goal of increasing nasal airway passages, preserving the function of the organ, minimizing perioperative hemorrhage, and long-term complications such as excessive nasal dryness, crusting, fetor, and the phenomenon known as the "empty nose syndrome."1,2

There is long-standing controversy among those who perform inferior turbinectomy over where and how much to excise during surgery. Clearly, the decision should be based not only on the clinical presentation but also on the histopathologic features of the organ. However, data on the latter are scarce and, when available, investigated as a side topic. The present study was undertaken exclusively to provide quantitative and qualitative information on various soft tissue and bony constituents of the hypertrophic IT. A comparison will be made between these findings and those obtained from a group of patients who had no clinical ITH.

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treatment with antihistamines, decongestants, topical corticosteroids, and mast cell stabilizers given for at least 2 months before the decision to operate was made. Immunotherapy for the patients with a known history of nasal allergy was ineffective or refused. Otherwise, participants were immunocompetent, generally healthy individuals. Given that allergy tests were not carried out in all cases, no differentiation was made between patients with or without allergy (ie, between patients with perennial allergic rhinitis and perennial nonallergic [vasomotor] rhinitis). None of the patients received topical or systemic corticosteroids or had symptoms of upper respiratory tract infection during the month before surgery. All patients underwent inferior turbinectomy that included removal of the bone and the surrounding mucosa. Patients who had septal deviation with contralateral compensatory ITH were excluded from the study.

The control group comprised 14 normal ITs. There were 2 pairs and 10 single samples retrieved from 8 men and 4 women in the course of septoplasty surgery. These patients had anatomico logically narrow nasal passages, and a satisfactory outcome of corrective surgery also required excision of the soft tissue and bony elements of the IT to increase airflow and improve nasal breathing. The group’s age ranged from 21 to 56 years (mean±SD age, 38.2±11.8 years). All patients had no clinical hypertrophy of the IT or history of nasal disease.

No significant difference in age was found between patients with ITH and normal controls (P =.06). Surgical procedures were performed between July 1997 and March 2002. All patients signed an informed consent form after being informed of the known benefits, risks, complications, and alternatives to surgery. The study protocol was approved by the institutional review board.

TISSUE PREPARATION

All samples were separately collected, underwent standard processing, and were investigated microscopically. Each sample had a well-defined conchal form with clear inferior, medial, and lateral portions of soft tissue and bony structure. The samples were fixed in buffered formaldehyde, thereafter decalcified with 0.7 M ethylenediamine tetra-acetic acid (EDTA) and dehydrated with increasing concentrations of ethanol. Then, each sample was aligned in the anteroposterior direction, measured, and cut into 3 equal parts, representatives of the anterior, middle, and posterior portions. The sections were embedded in paraffin blocks and serially cut into 5-µm-thick sections at a plane perpendicular to the mucosal surface. Every tenth section was stained with hematoxylin-eosin and mounted on a glass slide. For accurate comparisons, 1 section from each portion, positioned at the same distance along the course of the IT, was studied.

MEASUREMENTS

The dimensions of the anterior, middle, and posterior portions of the IT were recorded with a calibrated eyepiece attached to the microscope at original magnification ×40 and included the overall thickness of the IT, the thickness of the medial mucosal layer, the bone, and the lateral mucosal layer. The thicknesses of the epithelium, the basement membrane (BM), and the superficial lamina propria (LP) that houses the inflammatory cell infiltrate were also measured. Additional measurements of the superficial and deep borders of submucosal glands and venous sinusoïds and their corresponding thickness and the distance between the major arteries and the epithelial surface were also taken. Standard stereologic and morphometric methods were used to measure the relative proportions of the following soft tissue constituents: epithelium, connective tissue, gland, artery, and venous sinusoïd. A grid composed of 10×10 squares corresponding to 4 mm² surface area (2×2 mm) at original magnification ×40 was superimposed on the medial mucosal layer, the lateral mucosal layer, and the soft tissue beneath the bone (ie, the inferior mucosal layer). The soft tissue constituent that appeared at the upper left intersection of each square was recorded. This method allowed 300 hits on each portion and 900 hits on the entire sample. The relative proportion (ie, area fraction) of each constituent was calculated as the number of its cross points divided by the total points of the sample.

A qualitative assessment of the hypertrophic and normal sections was performed to indicate the possible presence of inflammation, venous sinusoïd engorgement, and fibrosis. Mason trichrome stain for collagen was used to demonstrate fibrosis.

STATISTICAL ANALYSIS

The paired t test was used to compare between the anterior and middle, anterior and posterior, and middle and posterior portions of the hypertrophic and normal ITs, and it showed that the differences between the portions were, overall, minute and insignificant. Thus, we decided to use the mean value of the measurements as representative of the 3 portions. The t test was then used to compare between various histologic and morphometric characteristics of the normal and hypertrophic ITs. Measurements were expressed as mean ± SD. A probability value of less than .05 was considered significant for age analysis. The Bonferroni correction was used to adjust for multiple comparisons, and statistical significance was set at P<.0012 (P<.05/42).

RESULTS

Table 1 lists the dimensions of the hypertrophic and normal IT. Although their height was similar, the hypertrophic IT was significantly wider than the normal IT (Figure 1). Further measurements show that the medial mucosal layer, which enlarged from 1.39±0.28 mm

| Table 1. The Dimensions of Hypertrophic and Normal Inferior Turbinates* |
|-----------------|-----------------|-----------------|-----------------|
| Patient Group   | Height          | Width           |                |
|                 | Overall         | IML             | MML Bone       |
| Hypertrophic (n = 20) | 7.82 ± 1.53 | 1.98 ± 0.72 | 2.53 ± 0.56 | 1.40 ± 0.44 | 1.26 ± 0.31 | 5.19 ± 0.60 |
| Normal control (n = 14) | 6.95 ± 1.64 | 1.53 ± 0.57 | 1.39 ± 0.28 | 1.16 ± 0.22 | 0.91 ± 0.26 | 3.42 ± 0.57 |
| P value         | .12             | .06             | ≤.001†         | .05          | .002         | ≤.001†       |

Abbreviations: IML, inferior mucosal layer; LML, lateral mucosal layer; MML, medial mucosal layer.

*Except for P values, all data are reported as mean ± SD millimeters. Measurements may not add up to totals because of rounding or incomplete data.

†Statistical significance.
to 2.53±0.56 mm ($P = .001$), made the greatest contribution to the total increase in the IT width (64.4%). The enlargement of the lateral mucosal layer from 0.91±0.26 mm to 1.26±0.31 mm was of borderline statistical significance ($P = .002$) and added only 19.8% to the total increase in the width. The contribution of the bone was relatively small and insignificant. Because of the minute and insignificant changes in the dimensions of the epithelium and the BM (data not presented), the increase in the width of the medial and lateral mucosal layers predominantly resulted from hypertrophic changes of the LP.

Further analysis disclosed that the portion of the medial, lateral, and inferior layers of the LP that houses subepithelial inflammatory cells significantly enlarged in patients with ITH compared with normal control subjects ($P = .001$ for each comparison). A similar increase was found in the portion of the medial and lateral layers for venous sinusoids and in the portion of the medial layer for submucosal glands (Table 2).

A morphometric analysis of the relative proportion of various soft tissue constituents (Table 3) shows that the connective tissue constituted the major component of the soft tissue, followed by venous sinusoids, submucosal glands, epithelium, and arteries. While the connective tissue, submucosal glands, and arteries did not undergo significant changes in patients with ITH, venous sinusoids increased significantly in all aspects of the hypertrophic mucosa. The epithelial area fraction of the inferior normal mucosa was also significantly greater than that of the hypertrophic one. Further analysis of the hypertrophic ITs indicates that the area fraction of serous glands was significantly greater than that of mucous glands in all aspects of the mucosa (Table 4).

**QUALITATIVE ASSESSMENT**

All hypertrophic ITs retained their basic mucosal architecture and had no evidence of tissue destruction.
Yet, to some extent, various changes from single to several abnormalities were noted. In some specimens, the affected area was confined to a small region, whereas in others it was more spacious. Similar to what has been observed in the normal IT, the epithelial layer was mainly composed of a pseudostratified columnar epithelium. In addition to deeply situated basal cells and superficially ciliated and nonciliated cells, it also housed an appreciable number of goblet cells. Small islands of metaplastic squamous epithelium were encountered in only 2 specimens. Areas of denuded epithelium were found in pathologic and normal specimens. High-power magnification revealed in part of the pathologic specimens a thin pinkish layer of plasma-derived gel created on the denuded BM. Fibrosis of the LP was the most common abnormality (18/20; 90%) affecting all aspects of the IT, with a greater propensity to involve the inferior mucosal layer (Figure 2). In some samples, the fibrosis was scattered all over the LP, whereas in others it appeared only in the superficial zone close to the epithelium. A marked subepithelial inflammatory cell infiltrate, which comprised a mixture of lymphocytes, macrophages, plasma cells, and eosinophils, was present in about two thirds of the samples (13/20; 65%) (Figure 3), and dilated and engorged thin-walled venous sinusoids in 3 (15%) (Figure 4). Neither edema nor dilated excretory glandular ducts were encountered in any of the samples.

A qualitative assessment of the 14 normal ITs revealed dilated venous sinusoids in 1 specimen. No other pathologic changes were found.

**COMMENT**

Chronic hypertrophic rhinitis is commonly associated with perennial allergic or nonallergic rhinitis. When these phenomena persist and the IT becomes hypertrophied and increasingly encroaches on the airway passages, nasal obstruction occurs. The data show that of all layers, the medial mucosa, which enlarges by 82% and adds 64.4% to the total increase in width of the IT, is the major contributor to the hypertrophy of the IT. The nasal airway passages extend from the septum to the medial mucosal layer; thus, relief of the obstruction mainly demands reduction of this layer. Nevertheless, its reduction carries increased risk of bleeding because of the relatively large branches of the sphenopalatine artery that emerge from the bone and traverse adjacent to the bone into the anterior portion of the medial mucosal layer.5

The popular practice of submucous resection of the bone, which dates back to the early 20th century,6 is still recommended as a treatment for ITH.7 Yet, except for the most anterior portion of the bone that is devoid of blood vessels5 and contributes to airway resistance,8 resection of this portion has no justification because it does not eliminate the main site responsible for ITH and nasal obstruction. Interestingly, in patients with compensatory ITH secondary to septal deviation, the main cause of IT expansion is the bone, whereas the contribution of the medial mucosa is insignificant.9 It should be remembered that different mechanisms are implicated in prolonged nasal obstruction originated from marked bilateral ITH and in compensatory ITH.

The measurement of various tissue constituents of the IT shows that the height of the epithelial layer in patients with ITH and in normal control subjects is simi-
lar, yet the area fraction of the inferior epithelial layer is significantly smaller in the former than in the latter. The source of this diversity can be explained by the fact that although the absolute height and the total surface area of the epithelial layer do not change, the LP enlarges, thus reducing the proportion of the area fraction of the epithelium in the hypertrophic IT. Lim et al.\textsuperscript{10} also reported similar epithelial thickness in patients with perennial allergic rhinitis and in normal subjects. With respect to the thickness of the BM, our measurements coincide with those of Lim et al.\textsuperscript{10} showing a close resemblance between patients with perennial allergic rhinitis and normal subjects. On the other hand, Sanai et al.\textsuperscript{11} reported significantly greater thickness of the BM in allergic patients compared with nonallergic ones. This disparity may be partly attributable to differences in methodology and sample characteristics. The superficial zone of the LP of normal control subjects houses various inflammatory cells that include lymphocytes, macrophages, monocytes, plasma cells, eosinophils, and mast cells.\textsuperscript{12,13} To assess the extent of the inflammatory cell infiltration, we measured the thickness of the area rather than carrying out an actual cell count of individual constituent. Although similar types of inflammatory cells were found in both groups, there was significant thickening of the superficial zone of the LP that is infiltrated with inflammatory cells in patients with ITH. The recruitment of these cells into the nasal mucosa is regulated by the production and release of various inflammatory mediators and cytokines.\textsuperscript{14} A comparison between the relative surface area occupied by IT submucosal glands in patients with ITH and normal subjects did not disclose significant difference in their density. Lin et al.\textsuperscript{15} found an increased number of submucosal glands in the IT of patients with chronic hypertrophic rhinitis and rhinitis medicamentosa compared with that of individuals with normal nasal mucosa, whereas others did not find similar differences between normal subjects and patients with perennial allergic rhinitis or chronic hypertrophic rhinitis.\textsuperscript{10,16} Furthermore, the density of serous glands in patients with ITH was significantly greater than that of mucous glands, whereas in normal control subjects the difference between the 2 types of glands was small and insignificant.\textsuperscript{12} These findings may point to greater formation of serous glands in the chronic inflammatory state. Contrary to what has been observed in submucosal glands, the relative surface area occupied by venous sinusoids in patients with ITH was significantly greater than that of normal control subjects in all turbinate surfaces. Schmidt et al.\textsuperscript{17} reported an increased number of blood vessels in the IT of patients with vasomotor rhinitis and related the phenomenon to formation of new vessels. On the other hand, the results of 2 other studies did not support a finding of greater vascular density in perennial allergic rhinitis.\textsuperscript{18,19}

Figure 3. A section from a patient with hypertrophic inferior turbinate showing marked subepithelial inflammatory cell infiltrate beneath the basement membrane (arrow), consisting of a mixture of lymphocytes, macrophages, plasma cells, and eosinophils (hematoxylin-eosin, original magnification ×200). E indicates epithelium.

Figure 4. A section from a patient with hypertrophic inferior turbinate showing dilated and engorged thin-walled venous sinusoids (arrows) (hematoxylin-eosin, original magnification ×100). E indicates epithelium.
Controversy surrounds the issue of nasal epithelial denudation. Gleich et al.\(^{20}\) were the first to ascribe epithelial denudation in the bronchi of asthmatic patients to the cytotoxic effects of eosinophil major basic protein. Similar epithelial pathologic changes were found in the sinuses of patients with chronic sinusitis\(^{21}\) and in the IT of patients with allergic rhinitis. Others failed to detect nasal epithelial denudation in allergic rhinitis.\(^{10,18,23}\) The issue becomes further complicated by the fact that Ordonez et al.\(^{24}\) suggested that loss of bronchial epithelium is merely an artifact of tissue sampling. We accomplished a qualitative assessment of the pathologic samples and found that large areas of the BM were completely denuded or had detached columnar cells, resulting in a single layer of basal cells covering the BM. These changes, although to a lesser extent, were also observed in the control group. An examination of the completely denuded areas with high-power magnification revealed that the denuded BM was partly covered with a thin pinkish layer of plasma-derived gel, a process that probably represents the first step of epithelial restitution.\(^{25}\) Thus, it may be concluded that epithelial shedding represents a genuine pathologic expression of disrupted mucosal barrier function.

Eighteen of 20 hypertrophic ITs (90%) displayed various degrees of fibrotic changes in the LP. Others also showed fibrosis in the IT of patients with vasomotor and chronic rhinitis, respectively.\(^{17,20}\) The scar tissue found in this process suggests a progressive and irreversible course, probably representing the end stage of inflammation. At this point, supportive treatment usually fails and the grounds for surgical reduction are laid down.

A limitation of the study is the lack of differentiation between perennial allergic and vasomotor rhinitis. Two previously reported studies from our group did not disclose significant differences in the population of mast cells and goblet cells between allergic and nonallergic patients.\(^{27,28}\) On the other hand, Schmidt et al.\(^{17}\) conducted a quantitative and qualitative assessment on fibrosis, edema, and blood vessels and reported different findings between the two. Possible differences between the dimensions of the IT in patients with perennial allergic and vasomotor rhinitis warrant further clarification. However, since each is a subset of chronic hypertrophic rhinitis and characterized by ITH, our goal to provide the surgeon with guidelines, practical tips, and a better understanding of IT reduction surgery is served.

In conclusion, on the basis of the current histopathologic and morphometric study of the hypertrophic IT, and similar to the assumptions laid out earlier,\(^{1,12}\) a number of clinical conclusions may be drawn. First, the targets for IT surgery are the medial and the inferior mucosal layers. The medial layer showed the greatest thickening, thus playing a major role in nasal obstruction. Although the inferior layer does not increase significantly, it is suitable for reduction because excision of an area (1) rich in venous sinusoids may avoid excessive congestion and obstruction, (2) poor in glandular elements does not increase the probability of nasal dryness, and (3) lacking major arteries does not increase the likelihood of perioperative hemorrhage. Second, the lateral mucosal layer should be spared during surgery. Although the enlargement of this layer was of borderline statistical significance, it (1) is rich in glandular tissue, (2) does not encroach on the airway, and (3) has an important role in humidifying the inspired air and maintaining the normal function of the mucociliary clearance system. Third, the bone should also be spared. It does not expand significantly and usually contains all main arteries in the posterior portion; therefore, its excision, except for the most anterior portion that is devoid of blood vessels, may expose the patient to the risk of perioperative hemorrhage. All these data show that total excision of the IT is not supported by the data. Fourth, the extensive fibrosis found in most hypertrophic ITs at the time of surgery points to the irreversible nature of chronic hypertrophic rhinitis.

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