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Review article

Effects of tonsillectomy and adenoidectomy on the immune system

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A B S T R A C T

Surgical removal of the tonsils and adenoids, important immune organs, is a frequent and recurrent class of surgery, and currently, there is no consensus on the effects these surgical procedures may have on the immune system. Here, we examine individual studies on tonsillectomy, adenoidectomy, and adenotonsillectomy, discuss their postoperative humoral and cellular immune changes, and explore their effects on the incidence of related diseases. There is evidence that these three surgeries have no negative effects on humoral immunity; however, there has been contrary results. Furthermore, these procedures seem to have no significant effects on cellular immunity, although tonsil and adenoid removal can cause an increased incidence of certain illnesses, especially infectious diseases. Based on this comprehensive review, we conclude that the removal of tonsils and adenoids does not negatively affect cellular and humoral immunity. However, surgery may lead to an increased incidence of related infectious diseases. This finding may inform the surgeon's decision to perform the procedure in a clinical setting.

1. Introduction

The pharyngeal tonsils (termed "adenoids") and palatine tonsils (termed "tonsils") are important lymphoid tissues located at the junction of the digestive tract and respiratory tract [1]. Together with the lingual tonsils, tubal tonsils, and lateral pharyngeal bands, they constitute the "Waldeyer's ring" [2]. The tonsils exist in pairs in the tonsil fossa, which is situated between the palatoglossal arch anteriorly, palatopharyngeal arch posteriorly, and the lateral wall of oropharynx [3]. Nevertheless, the adenoids are unpaired at the midline of the superior and posterior walls of the nasopharynx and are positioned near to both the sphenoid and occipital bones [4].

Histologically, the tonsils are relatively complex, covered with stratified squamous epithelium and invaginated to form 10–30 crypts. These lacunar-like crypts penetrate the lymphoid tissue, thereby increasing the contact area with antigens. The crypts themselves consist of stratified squamous epithelium and reticular crypt epithelium (also called lymphoepithelium), which are unevenly arranged. The lymphoepithelium is thin and lacks basement membranes in some areas, which allows foreign antigens to be transported and presented to lymphocytes quickly, thus effectively initiating the immune response. Furthermore, there are several tunnel-like intercellular channels between the epithelial cells. Some superficial channels open directly on the surface, whereas some channels are covered with flat microfold cells (M cells). As the tonsils have no afferent lymphatic network, the presence of crypts and M cells is particularly important for the regulation of immune functions. The adenoids are histologically similar to the tonsils but have few crypts, and their surface is covered with pseudostratified ciliated columnar epithelium [5].

As the tonsils and adenoids are the main components of Waldeyer's ring and located in a strategic position, they play a key role in providing immunity against alimentary and airborne pathogens, especially in children. The tonsils and adenoids are part of the mucosa-associated lymphoid tissue, which is a type of secondary lymphoid organ that provides a defensive barrier against pathogens [4]. The tissues begin to develop from birth, growing approximately 200 % in size by the age of 4–7 years, at which point the adenoids

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involute; however, the tonsils involute much later, starting at 14 years of age [6,7]. These two organs produce lymphocytes and antibodies, which are not only secreted to the surface—such as secretory immunoglobulin A—but also selectively migrate to secretory sites, such as the nasal mucosa and salivary and lacrimal glands, and continue to exercise humoral immunity [8–11]. T cells present in the tonsils and adenoids also play a meaningful role in fighting intracellular infection, tumor cells, and allogeneic cells, and their differentiation is affected by various factors, such as age, degree of infection, and antibiotic therapy [12]. In addition, tonsils express various antimicrobial peptides, including human β-defensin and cathelicidin human cationic antimicrobial protein-18, which are not only involved in antibacterial, immune, and inflammatory regulation but can also regulate adaptive immune responses [13–15]. However, there are some notable differences between tonsils and adenoids. In the adenoids, there are more potent B-cells, which help produce follicular T-helper cell populations. However, in the tonsils, biofilms form more easily that in the adenoids, and these can escape the host immune response, thereby facilitating the persistence and dissemination of bacteria in the tonsils [16–18].

Tonsillectomy is the surgical removal of the tonsils, including the tonsil capsule, by dissecting the peritonsillar space between the capsule and the muscle wall. Recurrent throat infection and obstructive sleep-disordered breathing are the two main surgical indications [19]. Adenoidectomy, the complete removal of adenoids, is usually performed to correct sleep-disordered breathing and nasal obstruction [20]. Although the incidence rates of tonsillectomy and adenoidectomy vary from region to region, altogether, this group of procedures represent one of the most common operations [19–22]. Given that the tonsils and adenoids are immunologically active lymphoid tissues, it is reasonable to hypothesize that their removal would have some adverse effect on the immune system; however, to date, no definitive conclusions have been drawn in this respect. Therefore, it is particularly worthwhile to review the effect of these operations on the immune system. In this review, we discuss the effects of tonsillectomy, adenoidectomy, and adenotonsillectomy on the immune system.

1.1. Effect of tonsillectomy on innate immunity

All subsets of granulocytes in the aging tonsils gradually accumulate, with basophils and mast cells being the most prominent. The increase in the frequency of mast cells in the tonsils may counteract the harmful excessive cellular immune response associated with autoimmunity. Therefore, tonsillectomies may have an impact on an individual's protection against inflammation and autoimmune diseases at a higher age [23].

1.2. Effect of tonsillectomy on humoral immunity

Recently, two systematic reviews were conducted on the effect of tonsillectomy on immunity, and, in each case, a conclusion was drawn: there is enough evidence to deduce that tonsillectomy has no significant negative impact on the immune system [24,25]. This is consistent with the results reported by Pidelaserra et al. [26]: no significant short or long term post-operative changes were reported in IgA, IgG, IgM, C3, and C4 levels. In addition, Pidelaserra et al. [26] showed that tonsillectomy did not cause any significant alteration in anti-influenza-specific serum titers after immunization with live attenuated influenza vaccine, which suggests that tonsillectomies would not affect humoral responses to this vaccination. Although the tonsil harbors the second most abundant lymphocyte, memory B cells, in various immune organs, the absence of the tonsils does not significantly affect the number of circulatory memory B cells. Moreover, the impact of tonsillectomy on the B cell memory function and response is also limited, as the absence of tonsils does not affect secondary tetanus toxoid responses [27].

However, there are reports of reduction in postoperative immune parameters. For example, in a long-term case-control study by Radman et al. [28], it was found that patients in the tonsillectomy group had significantly lower levels of IgG, IgA, and IgM than the non-tonsillectomized control group had, 4–6 years after operation. They reported that the CD10 expression as a B-cell indicator in patients with tonsillectomies was significantly lower than that in the control group, which perhaps indicates that the reduction in IgA, IgG, and IgM levels is caused by the decrease in B-cell count. Nasrin et al. [29] also found that IgG levels were significantly reduced at 3 months post-operation (but was still within the normal range); therefore, it was proposed that the immune status is not significantly altered.

The different findings of various studies may be due to the age of subjects, laboratory factors, and other characteristics of the patient population. It is difficult to limit the normal range of immune parameters, so it is particularly meaningful to set matched control groups. Notably, the decrease in the levels of immune factors after operation does not always mean an actual deficit of immune function [24]. In three recent studies we examined [26,28,29], there were no randomized controls with relatively small sample sizes; therefore, future studies may address this gap.

1.3. Effect of tonsillectomy on cellular immunity

Previous study findings indicate that tonsillectomies do not reduce cellular immunity, although the number of relevant published studies is limited. Randomized controlled studies are needed to reach a more definite conclusion. In a long-term study by Radman et al. [28], the T-cell counts of CD4, CD8, and CD56 did not change at 4–6 years after the operation. This would seem to indicate that tonsillectomy has no negative impact on cellular immunity in the long term. However, the short-term effects of tonsillectomy on cellular immunity still need to be studied.

1.4. Effect of tonsillectomy on the risk of developing certain diseases

Changes in the immune system may be reflected by the occurrence of certain diseases, such as infectious diseases, autoimmune diseases, and cancer. Currently, the findings regarding the relationship between tonsillectomy and the risk of these diseases are contradictory. A recent population-based cohort study revealed that tonsillectomy was associated with a nearly 3-fold risk of developing upper respiratory diseases [30]. On the contrary, another national cohort study found no difference in the number of visits for upper respiratory infections (URI) between the tonsillectomy and control groups; additionally, Chung et al. [31] found that tonsillectomy reduced the incidence of URI [32]. Park et al. [33] found no significant correlation between tonsillectomy and the incidence of pneumonia in adults, which indicates the age-related changes in tonsil immune function. The question remains, however, whether there is a relationship between tonsillectomy and pneumonia development in children.

Regarding deep neck infection (DNI), the results of two cohort studies indicated that infections significantly increased among patients who had undergone a tonsillectomy compared to those in the control group [34,35]. Frequent URIs have been shown to be a risk factor for developing DNI, which may explain the increase in the incidence of DNI after tonsillectomy [36]. In addition, Kim et al. [34] performed a subgroup analysis and found an increased risk of DNI, but almost exclusively in adolescents and adults. Patients with tonsillectomies may have reduced IgA levels, but the remaining mucosa-associated lymphoid tissue may compensate for the loss of tonsils [37]. It is supposed that the variation in compensatory capacity between children and adults has an impact on the rising risk of DNI in adolescents and adults [34]. Sex was also found to contribute to a difference in disease risk, as tonsillectomy was found to increase the risk of appendectomy due to appendicitis only in females and not in males [38].

In a national cohort study of autoimmune diseases following tonsillectomy, the incidence rates in 16 of 33 distinct diseases were found to have increased after tonsillectomy, and none of the diseases showed reduced incidence rates after the operation [39]. The thymus is known to be the site of extensive T-cell development and maturation, but there is also evidence that a stepwise program of T-cell development occurs within the human tonsils [40,41]. As a result, patients with tonsillectomies lose the ability to produce functional T cells, which may affect their immune systems and eventually lead to the development of some autoimmune diseases [39]. However, the results are inconsistent with respect to certain autoimmune diseases. For example, tonsillectomy was not found to be associated with disease risk, whereas a risk of multiple sclerosis (only among patients younger than 20 years old) has been reported [42,43]. Inflammatory bowel disease is a chronic inflammatory disease of the gastrointestinal tract that is thought to be caused by an interaction between environmental factors in genetically susceptible individuals and their intestinal mucosal immune system; there are two major disease phenotypes—Crohn's disease and ulcerative colitis [44]. A systematic review of the possible correlation between tonsillectomy and inflammatory bowel disease with its two disease phenotypes concluded that no obvious association between tonsillectomy and inflammatory bowel disease was identified in the meta-analysis [45]. In contrast, a significantly increased risk was observed in the case of Crohn's disease in another systematic review [46]. These contradictory observations suggest that more thorough research is needed to resolve these discrepancies.

Moreover, a national cohort study found that patients who underwent tonsillectomy had a 1.84-fold risk of developing irritable bowel syndrome compared to those without tonsillectomy and a 3.79-fold risk for those under 50 years old. The reason for this phenomenon may be that the absence of the tonsil may lead to undetectable pathogens entering the digestive tract, resulting in post infection irritable bowel syndrome or excessive growth of intestinal bacteria [47].

Tonsils are involved in immune defense, and their removal may impair immune monitoring and, thus, be associated with the development of cancer [4,48]. A recent population-based cohort study showed that tonsillectomy significantly increased the overall risk of developing cancer, subsequently, in the patients that were followed for more than three years. When a site-specific analysis was performed, this correlation was found to be significant only for breast cancer in females followed for more than three years [49].

1.5. Effect of adenoidectomy on humoral immunity

Although there are many similarities in the manner that the tonsils and adenoids perform their immune functions, there are still some differences that may cause the immune effects of adenoidectomy to differ from those of tonsillectomy [18]. The adenoids develop and enlarge during the first seven to eight years of life and then gradually degenerate, which may suggest that age at the time of adenoidectomy can alter the immune impact [50]. A study of children younger than 3 years of age showed that IgA levels decreased at 1 month postoperatively and returned to preoperative levels at 3 months postoperatively [51]. It is hypothesized that the immunity of the nasopharynx and oropharynx is probably dominated by humoral immunity and that IgA is one of the most important immune parameters [5]. Therefore, it is not surprising that there was a significant change in IgA levels only. In fact, the reduced levels of IgA were still within the normal range. Moreover, the elevation in IgA levels at 3 months postoperatively represents the remaining mucosa-associated lymphoid tissue to compensate for the loss of adenoids. Yan et al. focused on earlier postoperative effects in children younger than 3 years of age. They found elevated levels of IgA, IgG, IgM, C3, and C4 at 2 weeks postoperatively, compared to that in the controls and in the preoperative state [52]. This may have been be due to the activation of the immune system via the mechanical stimulation of the surgery itself and the antigens in the nasopharynx and oropharynx. These findings suggest that adenoidectomy has no significant negative impact on immunity.

Although both studies reached the above-mentioned conclusions, the small sample size may have been a limitation. Furthermore, there is a need for studies in other patient age groups. In addition, future focus should include the differences in surgical indications that might also affect preoperative immune levels, such as the differences in IgA levels in cases of exudative otitis media and in healthy children [53].

A bacterial biofilm is defined as a community of bacteria encased in a glycocalyx matrix of its own production. Adenoids have a

bacterial biofilm that may be associated with the development of certain diseases [54,55]. Mattila et al. [56] reported that adenoidectomy increased the risk of nasopharyngeal carriage of Streptococcus pneumoniae in children under 4 years of age, but this result was only observed in the first year after surgery; the concentration of pneumococcal polysaccharide antibody 6B decreased after 3 years of surgery. This finding suggests that adenoidectomy may have a negative impact, as prior knowledge has implied that adenoids may act as a reservoir of bacteria in upper airway infections and that nasopharyngeal colonization is strongly associated with nasal infections, possibly increasing the risk of invasive pneumococcal disease [55,57]. Another randomized controlled study found a small but detectable negative effect of adenoidectomy on the development of choline-binding protein A serum IgG antibodies to pneumococci in children, suggesting that adenoids may have a role in enhancing systemic immunity to pneumococci [58]. Mattila et al. [58] suggested that this "small but detectable effect" was probably caused by the fact that the average age of children in the study was 2 years old and that adenoidectomy at a younger age leads to more pronounced impairment of pneumococcal immunity.

1.6. Effect of adenoidectomy on cellular immunity

The surface secretions of the adenoids contain numerous activated T cells that are involved in cellular immunity along with certain cytokines [3]. In addition, when immune function decreases, it usually manifests as a decrease in $CD4^+$ T-cell count and an increase in $CD8^+$ T-cell count or a decrease in the CD4+/CD8+ ratio [52]. A study evaluating the immune effect two weeks after adenoidectomy showed that the levels of $CD3^+$, $CD4^+$, $CD8^+$, $CD56^+$, $CD3^+CD4^-CD8^-$, and $CD3^+CD4^+CD8^+$ were slightly increased compared to those during the preoperative period; the exception was $CD19^+$, which showed a slight decrease. However, none of these measures reached statistical significance, except for $CD3^+CD4^-CD8^-$, whose levels were increased both preoperatively and postoperatively compared to those in the control group. As with the above interpretation of the results for humoral immunity, the findings with respect to T cells may be due to antigenic and surgical stimulation. When comparing these results with the more pronounced response of humoral immunity in the same study, it appears that humoral immunity may be the primary immune response in the nasopharynx and oropharynx [52]. In another study wherein the immune effects were assessed at 1 and 3 months postoperatively, no meaningful changes were observed in immune parameters [51]. There are relatively few recent studies addressing the immune effects of adenoidectomy; therefore, a conclusion be drawn only with a larger number of comparable studies.

Effect of adenoidectomy on the risk of developing certain diseases.

To date, little research has been carried out on whether adenoidectomy is correlated with the risk of developing certain diseases. A cross-sectional study published in 2005 showed a correlation between previous adenoidectomy and subsequent appendicitis [59]. Regarding this result, Andreu et al. [59] speculated that it is the adenoidectomy that created a defect in the lymphoid tissue, forcing the remaining appendix to compensate in response to pathogens, thus making it more prone to inflammation and infection. In another large sample size cohort study, adenoidectomy was observed to be associated with an increased risk of developing chronic obstructive pulmonary disease, an upper respiratory disease, and conjunctivitis; however, an explanation for this association is lacking [30].

1.7. Effect of adenotonsillectomy on humoral immunity

Several recent studies have consistently agreed that adenotonsillectomy has no negative short or long term impact on humoral immunity in children; however, this does not indicate that immune parameters are not affected by adenotonsillectomy [60–62]. For example, in a longitudinal prospective study published in 2013, a significant decrease in IgA and IgG levels was observed 12–14 months after adenotonsillectomy, although it was still within the normal range of values; however, this result has not been clearly interpreted in the literature [62]. Notably, the subjects in this study that had significant changes in immune parameters were diagnosed with palatine and pharyngeal tonsil hypertrophy and prescribed adenotonsillectomy, whereas the subjects in two other studies, without significant changes in immune parameters, were diagnosed with obstructive sleep apnea hypopnea syndrome (OSAHS) and prescribed adenotonsillectomy. It is possible that the differences in surgical indications had some impact on the results of the study.

Immune activity is more important in children than in adults due to the incomplete development of systemic immune organs during childhood. Additionally, adenoids and tonsils develop most rapidly during childhood. To better understand the effects of adenotonsillectomy on humoral immunity, a study with subgroup analysis based on age may be helpful [50].

With the increased frequency of partial tonsillectomy in recent years, there has been a corresponding increase in the effects of: 1) partial tonsillectomy with adenoidectomy and 2) total tonsillectomy with adenoidectomy on humoral immunity [63,64]. In a study by Zhang et al. [64], it was found that 1 month after the subjects underwent partial tonsillectomy or total tonsillectomy, IgG, IgM, IgA, C3, and C4 levels were not significantly different from preoperative levels, indicating that both procedures did not negatively affect humoral immunity in the short term. However, in another study comparing the two procedures, also in patients with OSAHS, a different finding was reported. In that study published in 2014, patients in the complete tonsillectomy with adenoidectomy group showed significant reduction in the levels of IgA, IgG, and IgM at 1 month postoperatively compared to the preoperative levels, but the levels returned to preoperative levels at 3 months postoperatively. In contrast, patients in the partial tonsillectomy with adenoidectomy group showed only a slight and statistically insignificant decrease in humoral immunity levels after operation. This suggests that the residual tonsils still have some immune function and this may avoid postoperative immune deficiency; thus, there was confidence that partial tonsillectomy with adenoidectomy has some impact on immune function [63].

In addition, a study on the long-term effects of adenotonsillectomy on the atopic status of children showed that the operation did not alter their atopic status, and it was hypothesized that systemic atopy in children may be independent of the tonsil and adenoid tissue [65]. This study also reported that there were no significant differences in the expression of interleukin (IL)-2, IL-4, IL-5, IL-10, IL-13, IL-17, interferon (IFN)-γ, and tumor necrosis factor (TNF)-β cytokines between preoperative and postoperative patients with

adenotonsillectomy. Interestingly, in another study (published in 2019), in which the effect of adenotonsillectomy on cytokines was explored, a different result was obtained. This research found differences in high sensitivity C- reactive protein (hs-CRP), IL-1, IL-4, IL-10, IFN-γ, TNF-α, and intercellular adhesin molecule 1 (ICAM-1) levels between patients in the adenotonsillectomy and control groups [66]. However, postoperatively, none of the parameters were different from those of the control group, except IL-4, whose levels remained lower than those in the control group. This indicates that adenotonsillectomy has a positive effect in restoring abnormal inflammatory parameters to normal values in children with chronic tonsillitis or adenotonsillar hypertrophy or both [66].

1.8. Effect of adenotonsillectomy on cellular immunity

In general, recent adenotonsillectomy has been studied with respect to humoral immunity and—to a somewhat lesser degree—cellular immunity. These recent studies tend to conclude that adenotonsillectomy has no detrimental effect on cellular immunity in children, either in the short or long term [61–63]. Moreover, Santos et al. [62] found a significant increase in $CD4^+$ T cells at 1 month postoperatively, upon analysis at the subgroup level, and this was only evident for children aged 4 years and older. Interestingly, the risk of immune compromise at this age (four years and older) should theoretically be higher because of the more prominent immune activity of the tonsils during this period; however, no distinct explanation was provided. These results also supports the hypothesis that the effect of the patient age should be given more consideration when exploring the postoperative immune impact. In a previously mentioned study [63], wherein researchers analyzed the comparative immunological effects of partial tonsillectomy with adenoidectomy and total tonsillectomy with adenoidectomy, differences in cellular immunity parameters were not found to be meaningful. Only a slight decrease in CD4/CD8 values was observed at one month postoperatively, and these values recovered to preoperative levels at the third month postoperatively [63].

1.9. Effect of adenotonsillectomy on the risk of developing particular diseases

There are several studies on the changes in the incidence of URIs after surgery relative to that before surgery. Unlike adenoidectomy, which increases the risk of developing upper respiratory tract diseases, adenotonsillectomy has no significant effect on disease risk [30,67,68]. Furthermore, in the study by Tsou et al. [69] adenotonsillectomy was found to have a protective effect in children (reflected by fewer hospital visits for URI), and this effect was more pronounced in children under 12 years of age.

This apparent paradox—that adenotonsillectomy may either increase or decrease the risk of URI— can be explained in two ways. The tonsils and adenoids form the Waldeyer's ring, which may play a defensive role against URIs. Therefore, the surgical removal of these tissues may increase the risk of developing URI by altering the immune capacity [9,70]. Alternatively, URI is often considered an indication for adenotonsillectomy, so it seems plausible that the number of URIs would decrease after these operations [71,72]. Determining how to balance these opposing aspects, so that the benefits of adenotonsillectomy far outweigh its disadvantages, should be the focus of future research.

In addition, a study by Byars et al. [30] found a 17 % increased risk of infectious disease with adenotonsillectomy, and, additionally, an increased incidence of asthma and pneumonia in children has been found to be associated with adenotonsillectomy [68,73]. However, whether the increased incidence of these diseases is caused by immune alterations after adenotonsillectomy is not clear from these studies.

2. Conclusion

Overall, the results of most studies have shown that tonsillectomy, adenoidectomy, and adenotonsillectomy do not have significant negative effects on humoral immunity after surgery, but there are contrary results that exist. At a minimum, there seems to be a consensus that these three procedures have no effect on cellular immunity. The post-surgery period can be linked to changes in the incidence of many diseases, with infectious diseases being the main concern; both positive and negative outcomes have been reported, perhaps as a reflection of changes in immunity.

3. Outstanding questions

First, we found that more studies to date have tended to focus on parameters related to cellular and humoral immunity. Relatively few studies have been conducted on the effects of operations on non-specific immune and inflammatory responses. Therefore, we recommend measuring the intrinsic immune cells (e.g., phagocytes, killer cells, dendritic cells, etc.) and intrinsic immune molecules (e.g. complement, cytokines, enzymes, etc.) before and after operations. Second, we have found that discrepancies in results between similar studies may be due to differences between patient characteristics, such as age and indications for operation. We believe that categorizing and exploring this information appropriately may lead to a clearer conclusion. Third, as the extent of lymphatic tissue removed differs between tonsillectomy, adenoidectomy, and adenotonsillectomy, discussing these separately may help to draw clear conclusions. Fourth, the existing studies are predominantly retrospective, and we recommend more prospective and randomized controlled studies in the future to raise the level of evidence to a more convincing conclusion. Finally, many of the existing studies have small sample sizes and based on the abovementioned second and third points, we suggest that sample sizes should be increased depending on the subgroups in the study design and the study period length.

Data availability statement

This article is a review without research data. Data associated with our study has been deposited into a publicly available repository.

CRediT authorship contribution statement

Yueyang Liu: Writing – original draft. **Ting Liu:** Resources, Investigation. **Xinyi Li:** Resources, Investigation. **Tianshu Li:** Resources, Investigation. **Xiangchi Ma:** Validation, Formal analysis. **Dongxu Zhao:** Validation, Formal analysis. **Xueke Zheng:** Validation, Formal analysis. **Xudong Zhao:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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