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Review article

The effect of tonsillectomy on the immune system: A systematic review and meta-analysis

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ABSTRACT

Importance: The immunological sequelae of tonsillectomy in children have been a source of debate among physicians and a continuous concern for parents. Contradictory pertinent results exist in the literature.
Objective: To understand the real effect of tonsillectomy on the immune system.
Data sources: MEDLINE, EMBASE and COCHRANE.
Study selection: Articles addressing the effect of tonsillectomy on the immune system, up to Dec 2014. Related keywords and medical subject headings were used during the search. The abstracts were reviewed to determine suitability for inclusion based on a set of criteria. Manual crosscheck of references was performed.
Data extraction: We checked the tests results and the conclusion of each study to classify it as supporting or refuting the hypothesis of a negative effect of tonsillectomy on the immune system.
Results: We reviewed 35 articles, published between 1971 and 2014, including 1997 patients. Only Four studies (11.4%), including 406 patients (20.3%) found that tonsillectomy negatively affects the immune system. We performed a separate meta-analysis on various reviewed humoral and cellular immunological parameters (e.g. total and specific serum Ig's, SecIgA, cellular immunity, and Ag specific Ig). There is more evidence to suggest that tonsillectomy has no negative clinical or immunological sequalae on the immune system. Study limitations included heterogeneity in the diagnostic tools, timing of testing, indication for tonsillectomy and patients' age.
Conclusion: It is reasonable to say that there is enough evidence to conclude that tonsillectomy has no clinically significant negative effect on the immune system. It will be important for future studies to uniformly use both preoperative and control laboratory tests' levels to compare the postoperative levels with, to have short and long term follow-up levels, and to include both humoral and cellular immunity in their measurements.
Relevance: The results should reassure both surgeons and parents that tonsillectomy has no proven clinical sequalae. If more research is to be done in the future, it should be performed in a standardized way to avoid the heterogeneity seen in the literature.

Contents

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1. Introduction

Palatine tonsils produce antibodies via their B cells. Maximum tonsillar growth occurs between 4 and 7 years of age [1], while involution begins by the age of 14 years resulting in little lymphoid tissue remaining at the age of 60 years [2].

The immunological sequalae of tonsillectomy in children has long been a source of debate among physicians and a continuous concern for the parents. Many studies tried to understand the real effect of this common procedure on the various components of the immune system whether on the short or long term. This resulted in a heterogeneous pool of information sometimes creating confusion or uncertainty regarding this issue.

For that reason, we found it important to conduct a systematic review to carefully look at all the available studies and try to analyze the effect of tonsillectomy on each component of the immune system, hoping to answer the following questions: "does tonsillectomy negatively affect the immune system?","if it does, to what extent?", and "which components are mostly affected?"

2. Materials & methods

A MEDLINE, EMBASE and COCHRANE search was conducted to include all articles addressing the effect of tonsillectomy on the immune system, up to Dec 2014. Various related keywords and medical subject headings were used during the search; such as, (tonsillectomy AND humoral immunity) OR (tonsillectomy AND cellular immunity) OR (tonsillectomy AND immunity) OR (tonsillectomy AND Immune system).

The obtained titles and abstracts were reviewed to determine suitability for inclusion based on set criteria. Manual crosscheck of the included articles' references was performed. We excluded descriptive articles and narrative reviews, and patients duplicated in studies.

Inclusion criteria included: (1) aim of the study should be the effect of tonsillectomy with or without adenoidectomy on the immune system; (2) the study should measure quantitatively or qualitatively immunological factors; (3) the study should compare the obtained results to preoperative values and/or controls; (4) the study should be published in the English language.

A study was considered supporting the hypothesis that tonsillectomy has a negative effect on the immune system when the lab results confirmed that and the conclusion of the authors suggested that tonsillectomy has a negative impact on immunity or at least raised a significant concern regarding its negative effect on the immune system.

2.1. Statistical analysis

The reviewed studies addressed different parameters, so a meta-analysis could only be done on individual parameters, taking into consideration the different interpretations used among various studies. We tried, within the limitations of the information in each study, to classify the results as: no significant change (when no noticeable change in the level of the studied immunological factor is reported); decrease or increase to normal (when a noticeable change is reported); a significant decrease or increase (when statistically significant change is reported); below or above normal (when the level is reported as below or above the control levels and or a normal values' reference). We also looked at the effect of using controls vs. only using preoperative values to compare and report results.

The result of each individual meta-analysis was reported as a percentage of studies (including percentage of enrolled patients) showing negative vs. no effect (or positive) on the particular immunological factor. Comparison was made between both groups within the same meta-analysis with respect to age range, duration of follow-up and presence of control group.

3. Results

The process of articles' screening and selection is summarized in Fig. 1. We searched the articles that were written in the English literature, with available abstract and including only studies conducted on humans.

We reviewed 35 articles, published between 1971 and 2014 [3–37]. These included 1997 patients, aged 1.5 to 55 years. Seven studies included patients older than 18 years in conjunction with pediatric patients. We could not isolate the data of the pediatric patients from those of adults within each of these articles, so we kept them combined and pointed to any reported difference in results within each article, where applicable. Another reason we did not exclude these studies is the fact that some included different age groups for comparison which was quite useful [8,10,25], while others looked at the sequalae of tonsillectomy in young adults who had tonsillectomy in the past [11]. The timing of postoperative testing varied from 10 days to 11 years, with 2 studies not specifying the timing. This variation in timing provided information about the short and long-term immunological consequences of tonsillectomy. The indication for tonsillectomy was recurrent or chronic tonsillitis in 14 studies, adenotonsillar hypertrophy in 5, both indications in 11 and unspecified in 5. The distribution of the various studied parameters among the reviewed manuscripts is summarized in Fig. 2.

Based on the conclusion of each study and taking into consideration the tests' values and their clinical significance where applicable, we could classify 4 studies as implying a negative impact of tonsillectomy on the immune system or at least raising a significant concern regarding its negative effect on immunity. Table 1 summarizes the various tests performed, and the conclusion of each study. The results were divided into 2 groups: one studying the effect of tonsillectomy on the humoral immunity (Table 2) and another studying the effect of tonsillectomy on the cellular immunity (Table 3).

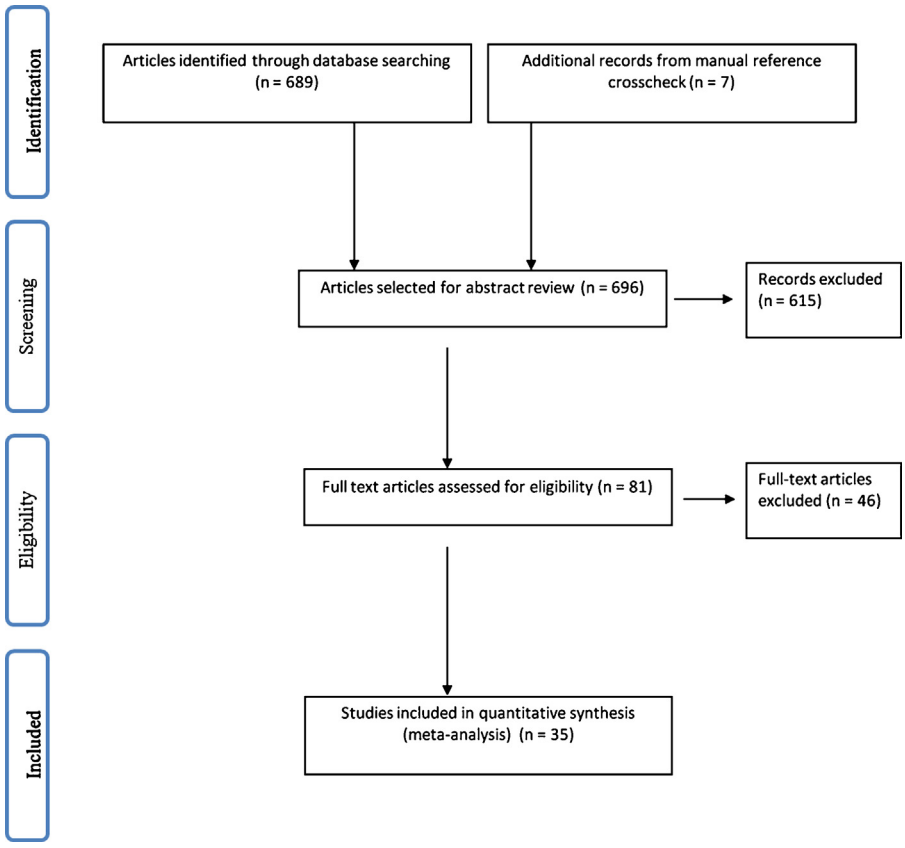

Fig. 1. Flow diagram describing the strategy used to include the articles in the review.

3.1. Humoral immunity

3.1.1. Serum immunoglobulins

Twenty six manuscripts (enrolling 1713 patients) studied the effect of tonsillectomy on serum Ig's (3 studies looked at IgA only, one omitted IgA). Five studies (19.2%) demonstrated a significant drop or low level of one or more serum Ig's postoperatively (Table 2). These included 794 patients (46.35%) with age range of 1.5-24 with postoperative testing performed between 4 and 132 months, with a mean of 49 months which is significantly longer than the 14 months mean follow-up of the remaining 21 studies.

Looking specifically at the Ig's types, we found basically the same trend:

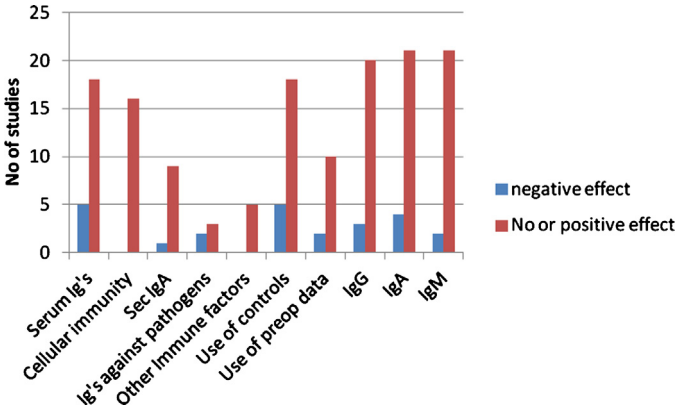

Fig. 2. Distribution of the studied parameters.

3.1.1.1. Serum IgG. Of the 23 studies that looked at the effect of tonsillectomy on IgG (Tables 1 and 2), only 3 demonstrated a negative effect (360 patients or 29.7%), having a postoperative testing at a mean of 21.3 months (vs. 14.9 months). However, that was not clinically significant in one study (Friday et al.) and another one did not have a control group (Cantani et al. [15]).

3.1.1.2. Serum IgA. The effect of tonsillectomy on serum IgA was studied in 25 manuscripts (Tables 1 and 2). Significant drop in level was reported in 4 studies (one without control group) (526 patients or 31.2%); however, that was not clinically significant in one of them (Böck et al. [22]). These 4 studies had the postoperative testing done at a mean of 55.3 months vs. 13.2 months for the rest of the studies.

3.1.1.3. Serum IgM. 23 studies addressed the effect on serum IgM (Tables 1 and 2). Only 2 studies reported a significant drop in level. These included 92 patients (7.6%) and had the postoperative testing done at a mean of 17 months vs. 14.7 months for the rest of the studies.

3.1.2. Secretory IgA

The effect of tonsillectomy on SecIgA level was studied in 10 manuscripts (Table 2). All but one study, showed either no or positive effect. This single study had no controls and had the postoperative testing done at 4 months.

3.1.3. Immunoglobulins against pathogens

Five studies looked at the effect of tonsillectomy on immunity against certain pathogens (Tables 1 and 2). Two of them (40%) showed a significant drop in specific Ig's. these included 65 patients (40.6%) with age range of 3–34 years (vs. 2–12.8 years)

Table 1
Summary of the reviewed articles.

Authors	C	Performed tests	Conclusion
(1) Ogra (1971)	Yes	Serum and nasopharyngeal Ig's to polio virus	Tonsillectomy impairs development and maintenance of Ig's in nasopharynx against polio virus
(2) Veltri et al. (1972)	No	Serum IgG, IgM, IgD, IgA; SecIgA, Ig's to viruses	Tonsillectomy doesn't modify host's systemic immunological competence
(3) Donovan and Soothill (1973)	Yes	Serum IgG, IgA, IgM, IgE; SecIgA; delayed hyper-sensitivity skin test; ASO titer; lymphocyte activity	The low IgA was not due to tonsillectomy but to a primary minor immune deficiency in IgA
(4) Ostergaard (1977)	Yes	Serum and salivary IgG, IgM, IgA; Serum IgE	The decrease in IgG and IgM are either due to removal of chronically infected organs or important immunological tissue.
(5) Gogoi et al. (1979)	Yes	Serum IgG, IgM, IgA, lymphocytes count, skin tests with candida, PPD and DNCB	No significant variations in Ig's levels. Improved cell mediated immunity postop.
(6) Virolainen et al. (1980)	No	WBC count and activity, serum IgA, IgG, IgM; Cell-mediated immune response	All parameters studied were normal preop and postoperatively
(7) El-Ashmawy et al. (1980)	Yes	Serum IgA, IgG, IgM, IgD	Tonsillectomy does not seem to compromise immunological integrity
(8) Yamauchi et al. (1981)	Yes	Serum IgG, IgA, IgM, Serum humoral factors (α macroglobulin, α1 acid-glycoprotein, ceruloplasmin, haptoglobin, transferrin, α1 anti-trypsin, C3c), response of lymphocytes to mitogens	No negative effect in general
(9) D'Amelio et al. (1982)	Yes	Serum and salivary IgA	The role of tonsillectomy in serum IgA deficiency is still unclear
(10) Prusek et al. (1983)	Yes	Percentage of T and B lymphocytes	Tonsillectomy leads to normalization of B and T lymphocytes' distribution
(11) Lal et al. (1984)	Yes	IgA, IgG and IgM; ESR level	Tonsillectomy does not adversely affect the humoral immune system
(12) Siegel et al. (1984)	No	Lymphocyte trans-formation test; suppressor index	No specific effect on the stimulating or suppressor cell activity of peripheral lymphocytes
(13) Cantani et al. (1986)	No	Serum IgM, IgA, IgG, SecIgA	Serum Ig's and SecIgA levels significantly decreased 1 and 4 months postoperatively
(14) Bussi et al. (1991)	No	Peripheral blood and tonsillar mononuclear cells	Tonsillectomy can be performed without creating systemic disorders in the immune response
(15) Friday et al. (1992)	Yes	IgA, IgG, IgM levels	A decline in serum Ig's following tonsillectomy appears not to be a risk factor for developing throat infection, and may reflect a reduction in antigenic stimulation.
(16) Lenander-Lumikari et al. (1992)	Yes	Salivary IgA, IgG, and IgM; salivary antimicrobial proteins lactoferrin, salivary peroxidase, myelo-peroxidase; antibodies against viral antigens and strep mutans	Tonsillectomy does not affect the humoral immune response of individuals
(17) Moreno et al. (1992)	No	Mitogenic response to PHA, ConA, and PWM	Decrease in stimulation index to PHA, ConA and PWM after tonsillectomy reflecting a decrease in lymphocyte stimulation by bacteria postoperatively
(18) Sainz et al. (1992)	No	Serum IgA, IgG, IgM and IgE and complement factors 3, 4 and PFB	Tonsillectomy has no counter-productive effect on the immune system. It actually improves the immune response unblocking the suppression to which it was subject.
(19) Sennaroglu et al. (1993)	Yes	Neutrophil chemo-taxis function	Tonsillectomy restores the deficiency in the neutrophil chemotaxis
(20) Böck et al. (1994)	Yes	white cells count, lymphocyte subpopulation, IgM, IgA, IgG, IgE and light chains kappa and lambda	Tonsillectomy may lead to changes in the cellular and humoral immune systems, but are clinically insignificant
(21) Del Rio-Navarro et al. (1995)	No	Serum IgA, IgG and IgM, SecIgA	Tonsillectomy does not affect the humoral immune system
(22) Kirstila et al. (1996)	No	Salivary Ig's (IgA, IgG, and IgM), anti-Streptococcus mutans, anti-viral Ig's, lysozyme, lactoferrin, peroxidase, agglutinin	Tonsillectomy does not seem to lead to any significant long-term impairment of salivary defense capacity.
(23) Jung et al. (1996)	Yes	Serum IgA, SecIgA; densities of IgA immunocytes inside tonsillar tissue	No significant changes in the local immune system after tonsillectomy
(24) Jurkiewicz et al. (1997)	Yes	Serum IgA, IgG, IgM CD3, CD4, CD8, Multitest CMI	No persistent negative effect on the immune system
(25) Childers et al. (2001)	Yes	SecIgA, Ag-specific Ig's in saliva and serum	Non-significant decrease in SecIgA and serum IgA and IgG levels after tonsillectomy
(26) Zielnik-Jurkiewicz & Jurkiewicz (2002)	Yes	Serum IgA, IgM, IgG, CD3, CD4, CD8 and CMI	Though tonsillectomy caused statistically significant decrease of the values of immunity parameters in the early period. These normalized after 6 months.
(27) Ikinciogullari et al. (2002)	Yes	Serum IgG, IgA, IgM, total lymphocyte counts. lymphocyte subsets and activation markers	Tonsillectomy does not cause significant changes in the immune system
(28) Kaygusuz et al. (2003)	Yes	Serum IgG, IgM, IgA; C3 and C4; CD3, CD4, CD8, CD19, CD25, CD16	Tonsillectomy restores the immune parameters by removal of bacterial stimulus without negatively affecting the patient's immune functions
(29) Van den Akker et al. (2006)	Yes	Serum IgA, IgG, IgM	The decrease within normal levels is compatible with a reduction of antigenic stimulation.
(30) Baradaranfar et al. (2007)	Yes	Serum IgM, IgG; TL (CD3), TH (CD4), TC (CD8) BL (CD20)	No negative effect on immunity
(31) Kaygusuz et al. (2009)	Yes	Serum IgG, IgM, IgA; C3 & C4; CD3+,4+,8+,19+,25+,16++,56+)	Tonsillectomy does not compromise immune function

Table 1 (*Continued*)

Authors	C	Performed tests	Conclusion
(32) Nasrin et al. (2012)	Yes	Serum IgG, IgM, IgA	Humoral immune system was not significantly altered after tonsillectomy
(33) Santos et al. (2013)	No	Serum IgA, IgM, IgG; Lymphocyte count	Neither humoral nor cellular immune systems were affected by tonsillectomy
(34) Pidelaserra Marti et al. (2014)	No	Serum IgG, IgM, IgA	Tonsillectomy does not compromise systemic humoral immunity nor the specific immunoglobulin response to influenza vaccination.
(35) Dai et al. (2014)	No	Serum IgG, IgM, IgA	Partial tonsillectomy by plasma-mediated temperature-controlled radiofrequency ablation did not impact on the humoral immunity of children.

C, controls; Ig, immunoglobulin; Sec, secretory.

Table 2
Effect of tonsillectomy on the humoral immune system.

Study	No/I	Age (y)	Preop/ postop testing	F/U up to (months)	C	Result				
						Path.	IgG	IgM	IgA	SecIgA
(1) Ogra P L	40/?	3–11	+/+	7	+	**Sign ↓ to < Nl**				
(2) Veltri et al.	17/T	2–10	+/+	12	–	No sign Δ	Sign ↓ to Nl	No sign Δ	No sign Δ	No Δ
(3) Donovan and Soothill	36/T	3–12 y	+/+	6	+		Nl level	Nl level	**Low level preop**	Nl level
(4) Ostergaard PA	27/T	6–11	+/+	30	+		**Sign ↓ to < C levels**	**Sign ↓ to < C level**	**Sign ↓ to < Nl**	Sign ↑ to Nl
(5) Gogoi et al.	80/T	5–14	+/+	3	+		No sign Δ	No sign Δ	No sign Δ	
(6) Virolainen et al.	17/T	10 & 20	+/+	1/120*	–		No sign Δ	No sign Δ	No sign Δ	
(7) El-Ashmawy et al.	10/T	5–14	+/+	2	+		Sign ↓ to Nl	No sign Δ	Sign ↓ to Nl	
(8) Yamauchi et al.	54/T, TH	4–55, <8, 9–15, >16	+/+	–	+		No sign Δ+	No sign Δ+	No sign Δ+	
(9) D'Amelio et al.	274/?	16–24	−/+	–	+				**Sign < C$**	No sign Δ
(10) Lal et al.	40/T	5–15	+/+	1	+		Sign ↓ to Nl	No sign Δ	No sign Δ	
(11) Cantani et al.	65/T, TH	2–11	+/+	4	–		**Sign ↓ to < Nl**	**Sign ↓ to < Nl**	**Sign ↓ to < Nl**	**Sign ↓ to < Nl**
(12) Friday et al.	268/T, TH	1.5–16	+/+	30	+		**Sign ↓ to < Nl++**	No sign Δ	No sign Δ	
(13) Lenander-Lumikari et al.	53/?	5–8	−/+	48	+	↑ in anti viral Ig's				Sign ↑ to > Nl#
(14) Sainz et al.	30/T	5–10	+/+	1	–		↓ in level but still Nl	↓ in level but still Nl	↓ in level but still Nl	
(15) Böck et al.	160/T	4–8	−/+	132	+				**Sign < C^**	
(16) Del Rio-Navarro et al.	33/T, TH	3–13	+/+	>3	–		Sign ↓ to Nl	Sign ↓ to Nl	Sign ↓but still Nl	Sign ↑
(17) Kirstila et al.	25/T, TH	15–34	+/+	6	–	**Sign ↓in anti SM IgG & anti EBV Ig's**				No Δ**
(18) Jung et al.	66/T, TH	<4- > 19	+/+	1	+				↓ to C levels	Sign ↓ to Nl
(19) Jurkiewicz et al.	30/TH	3–14	+/+	3	–		Sign ↓ to Nl	Sign ↓ but still Nl	Sign ↓but still Nl	
(20) Childers et al.	25/T, TH	4.4–12.8	−/+	6	+	↑activity of antigen specific SecIgA				No sign Δ
(21) Zielnik-Jurkiewicz and Jurkiewicz	80/TH	3–14	+/+	6	+		Sign ↓ to Nl	Sign ↓ to Nl	↓to C levels	
(22) Ikinciogullari et al.	15/T	4–10	+/+	2.5	+		No sign Δ	No sign Δ	No sign Δ	
(23) Kaygusuz et al.	37/T	5–9	+/+	1	+		Sign ↓ to Nl	Sign ↓ to Nl	Sign ↓ to C levels	
(24) Van den Akker et al.	123/T, TH	2–8	+/+	12	+		↓ to Nl	No sign Δ	No sign Δ	
(25) Baradaranfar et al.	30/T, TH	4–10	+/+	6	+		Sign ↓ to Nl	No sign Δ		
(26) Kaygusuz et al.	20/T	5–9	−/+	54	+		No sign Δ	No sign Δ	No sign Δ	
(27) Nasrin et al.	70/T, TH	<18	+/+	3	+		Sign ↓ to Nl	No sign Δ	No sign Δ	
(28) Santos et al.	29/TH	2–8	+/+	14	–		Sign ↓ to Nl	No sign Δ	Sign ↓ but still Nl	
(29) Pidelaserra Marti et al.	45/T, TH	3–17	+/+	12	–		No sign Δ	No sign Δ	No sign Δ	
(30) Dai et al.	57/TH		+/+	3	–		No sign Δ	No sign Δ	No sign Δ	

Ig, immunoglobulin; Preop, preoperatively; Postop, postoperatively; F/U, follow-up; Sign, significant; I, indication; T, tonsillitis; TH, tonsillar hypertrophy; Path, immunoglobulin against pathogens; Nl, normal; Δ, change; C, control;?, not specified; SM, streptococcus mutans.

* The 10 yo children had the tests done 1month preop and 1 month postop; the 20 yo young adults had only tests done 10 y after their tonsillectomy.

+ Low level pre-existed preop in children <8 yo.

$ No clinical data to conclude significance.

++ Yet clinically insignificant (rate of infections postop was much more less than in controls).

Salivary IgG & IgM were also tested and they significantly increased postop.

^ The drop was clinically insignificant.

** Salivary IgG & IgM were also tested and they significantly decreased postop.

Table 3
Effect of tonsillectomy on cellular immunity.

Study	No of patients	Age range (y)	Preop/postop testing	F/U up to (months)	Controls	Indication for tonsillectomy/result
(1) Gogoi et al.	80	5–14	+/+	3	+	Tonsillitis/improved cell-mediated immunity. Lymphocytes count decreased to normal
(2) Virolainen et al.	17	10 & 20	+/+	–	–	Tonsillitis/no sign change
(3) Yamauchi et al.	54	4–55, <8, 9–15, >16	+/+	–	+	Tonsillitis, tonsillar hypertrophy/response of lymphocytes to mitogens increased to normal*
(4) Prusek et al.	50	5–15	+/+	10	+	Tonsillitis/Restoring percentage of T & B lymphocytes
(5) Siegel et al.	12	15–45	+/+	2.5	–	Not specified/no sign change
(6) Bussi et al.	40	3–30	+/+	3	–	Tonsillitis, tonsillar hypertrophy/no sign change
(7) Moreno PM et al.	27	5–10	+/+	1	–	Tonsillitis/decrease in stimulation index but within normal
(8) Sennaroglu et al.	17	4–11	+/+	0.3	+	Tonsillitis/neutrophil chemotaxis improved postop
(9) Böck et al.	160	4–8	−/+	132	+	Tonsillitis/no sign change
(10) Jurkiewicz et al.	30	3–14	+/+	3	–	Tonsillar hypertrophy/no sign change
(11) Zielnik-Jurkiewicz and Jurkiewicz	80	3–14	+/+	6	+	Tonsillar hypertrophy/normalization postop
(12) Ikinciogullari et al.	15	4–10	+/+	2.5	+	Tonsillitis/normalization postop
(13) Kaygusuz et al.	37	5–9	+/+	1	+	Tonsillitis/normalization postop
(14) Baradaranfar et al.	30	4–10	+/+	6	+	Tonsillitis, tonsillar hypertrophy/normalization postop
(15) Kaygusuz et al.	20	5–9	−/+	54	+	Tonsillitis/no sign change
(16) Santos et al.	29	2–8	+/+	14	–	Tonsillar hypertrophy/sign increase in T helper cells

Preop, preoperatively; postop, postoperatively; F/U, follow-up; sign, significant.
* except in children < 8 yo.

and postoperative testing performed at a mean of 6.5 months (vs. 24.7 months).

3.1.4. Other humoral factors

Other factors (e.g. complement system factors) were studied in 5 articles (Yamauchi et al. [10], Lenander-Lumikari et al. [18], Sainz et al. [20], Kirstila et al. [24], Kaygusuz et al. [30]). None of the studies showed a negative effect of tonsillectomy.

3.2. Cellular immunity

Cellular immunity was studied in 16 manuscripts (Table 3). These included 698 patients, with age range of 2–45 and a postoperative testing occurring at up to 132 months (mean 17 months). All these studies not only showed no negative effect but some also showed a positive effect on cellular immunity in the enrolled patients.

3.3. Control levels

Twenty-three studies used controls to compare their postoperative results to (Table 1). Only 5 studies (21.8%) found a decrease in the level of tested immunological parameters compared to controls; however, 2 of them (Friday et al. [17], Böck et al. [22]) had clinically insignificant decrease in the levels. So, if we follow the way we classified the reviewed studies, we can consider only 3 controlled studies (341 patients or 27.6%) pointed at a negative effect of tonsillectomy on immunity.

3.4. Preoperative levels

Twelve studies were not controlled and used the preoperative values as a reference to compare the postoperative levels to (Table 1). Only 2 studies (including 90 patients or 23%) showed a negative effect on the immune system. The postoperative testing was performed at a mean of 5 months compared to 15.9 months in the other studied groups.

4. Discussion

The main challenge in such a review is the heterogeneity of the studies. Though the main aim of all the studies is to analyze the effect of tonsillectomy on the immune system, there was no unified method to conduct that. There was variability in the used tests (Table 1), the age range of the enrolled patients (Tables 2 and 3), the timing of postoperative testing (Tables 2 and 3) and the indications for tonsillectomy.

Another major issue is the absence of uniform normal range values for the performed tests, among the studies. These values can vary depending on the age range of the patients, the laboratories performing the tests, and the patients' population. A compensation for that will be using a matching control group. Around 2/3 of the studies used a control group and most of these (19 out of 23) did not demonstrate or support a negative effect of tonsillectomy on the immune system, which was quite re-assuring.

Those who did not have a control group used the preoperative values for comparison (Tables 2 and 3). A decrease in the immunological factors' values postoperatively did not always mean a drop in immunity. Veltri et al. [4], for instance, did not use a control group and noticed a significant decrease in IgG levels postoperatively, but that decrease was to normal levels, meaning that the preoperative levels were abnormally elevated. On the other hand, Donovan and Soothill [5] noticed abnormally preoperative low levels of serum IgA in their patients, which persisted postoperatively. Having preoperative levels is therefore crucial to rule out pre-existing deficiencies in immunity.

The effect of tonsillectomy on the level of serum Ig's was the most studied. The initial results raised some concerns, as almost half of the enrolled patients had a significant decrease of one or more Ig level postoperatively over an extended follow-up period (mean 49 months). When we looked closely at the individual Ig's changes and their clinical significance, the picture looked different.

The IgG level was measured in 23 manuscripts, 3 of which showed a significant decrease postoperatively. However, the largest study among these three (Friday et al. [17]) did not find any clinically significant sequalae (e.g. no increase in postoperative subsequent throat infections) and concluded that this change is due to a reduction in antigenic stimulation.

Serum IgA was the most studied. The postoperative laboratory results of 4 studies raised concerns regarding the long term effect of tonsillectomy on serum IgA levels, especially that the testing was done at a mean of 55.3 months postoperatively. However, the clinical sequalae of that decrease was not clear. In the largest of these studies (D'Amelio et al. [11], 274 patients) the clinical

relevance was not studied and in the 2nd large study (Böck et al. [22], 160 patients) the results were clinically insignificant.

The changes in IgM levels were well studied and the effect of tonsillectomy on it was found negligible, as only 2 studies, including 8.6% of the patients in this category, showed a significant drop in levels. One of these studies had no control group to compare with. These findings are reassuring regarding the effect of tonsillectomy on the humoral immunity, as IgM is the 1st Ig to appear in the response to an acute antigenic stimulation.

Moreover, the reviewed studies showed no concerns regarding the effect of tonsillectomy on the level of SecIgA, and other studied humoral factors (e.g. salivary humoral factors, complement system factors), which refutes the old suspicions that tonsillectomy may result in more MALT related infections.

What was interesting in this review is the finding that no study showed a negative effect on the cellular immunity. In fact, there was evidence of a positive sequalae of tonsillectomy on the cellular immune system (Table 3). Many studies showed that cellular immunity normalized postoperatively. For example, Yamauchi et al. [10] showed an increase in response of lymphocytes to mitogens (back to normal), while Sennaroglu et al. [21] demonstrated an improvement of neutrophil chemotaxis postoperatively.

The real clinical effect of tonsillectomy on the overall function of the immune system may be reflected in its effect on the incidence of graft vs. host disease in those patients who undergo tonsillectomy prior to bone marrow transplantation. It was interesting to see that tonsillectomy does not have an impact on the incidence according to a study by Schwab and Raynor at Duke University [38]. This is quite reassuring especially that the studied group is quite vulnerable immunologically.

If tonsillectomy were detrimental on the general immune system, one would expect that common pathogens are more prevelant in those who had undergone tonsillectomy. An example of an appropriate pathogen to conduct such a study on would be the Epstein–Barr virus, because it is ubiquitously present in 95% of the adult population. Interestingly, In a study by Durovic et al. [39] investigating the factors that help an individual to be in the 5% of the population that are not infected by that virus, it was found that a history of tonsillectomy correlated well with not being a carrier of the virus. This is yet another reassuring result that the immune system remains clinically intact after the removal of the tonsils.

5. Conclusion

Though the reviewed studies had variability in many aspects, it is reasonable to say that there is enough evidence to conclude that tonsillectomy has no clinically significant negative effect on the immune system. It will be important for future studies to uniformly use both preoperative and control laboratory tests' levels to compare the postoperative levels with, to have short and long term follow-up levels, and to include both humoral and cellular immunity in their measurements.

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Contributor's statements

Mohamad A. Bitar: Dr Bitar conceptualized and designed the study, drafted the initial manuscript, performed the analysis and approved the final manuscript as submitted.

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