

# Alterations in Humoral Immunity After Partial Versus Total Tonsillectomy: A Pilot Study and Systematic Review of Literature

Mohamad A Bitar,<sup>1,2,3,4,\*</sup> Charbel Rameh,<sup>1,5</sup> Nour F Ataya,<sup>6</sup> Alik Najarian,<sup>5,6</sup> Marita Chakhtoura,<sup>6</sup> and Alexander Abdelnoor<sup>6</sup>

<sup>1</sup>Department of Otolaryngology Head and Neck Surgery, American University of Beirut, Faculty of Medicine and Medical Center, Beirut, Lebanon

<sup>2</sup>Department of Pediatrics and Adolescent Medicine, American University of Beirut, Faculty of Medicine and Medical Center, Beirut, Lebanon

<sup>3</sup>Department of ENT Surgery, The Children's Hospital at Westmead, Sydney University, Sydney, Australia

<sup>4</sup>Pediatric Otolaryngology Program, Al-Jalila Children's Specialty Hospital, Dubai, UAE

<sup>5</sup>Private Practice, Beirut, Lebanon

<sup>6</sup>Department of Microbiology, American University of Beirut, Faculty of Medicine and Medical Center, Beirut, Lebanon

\*Corresponding author: Mohamad A Bitar, Pediatric Otolaryngology Program, Al-Jalila Children's Specialty Hospital, Dubai, UAE. Tel: +97-142811203, E-mail: mbitar-md@hotmail.com

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## Abstract

**Background:** The palatine tonsils are secondary lymphoid organs, important in sampling antigens directly from the epithelial surfaces. They produce antibodies locally and distally through their migrating B cells.

**Objectives:** The aim of this study was to compare the changes in serum and saliva immunoglobulin (Ig) levels after total vs. partial tonsillectomy and also to systematically review the literature regarding the changes in humoral immunity following tonsillar surgery.

**Patients and Methods:** Children with obstructive tonsils were recruited in a pilot study and randomized to undergo total or partial tonsillectomy. Blood and saliva samples were obtained immediately preoperatively and within 3 months postoperatively, to measure serum Ig (G, M and A) and saliva secretory IgA concentrations. Patients' clinical history was reviewed at one year postoperatively. Systematic literature review regarding the effects of tonsillar surgery on humoral immunity was performed, using Medline, Embase and Cochrane.

**Results:** Nineteen patients completed the study (11 partial, 8 total). No statistically significant changes noted in the serum Ig's level in both groups, except for IgM which increased ( $P = 0.018$ ) after partial tonsillectomy, mainly in males ( $P = 0.04$ ), and in those aged 5 years and older ( $P = 0.02$ ). There was noticeable decrease in susceptibility to infections. Four out of 30 studies (406 out of 1796 patients) showed decrease in some elements of the humoral immunity or suspected a negative impact of tonsillectomy on the immune system.

**Conclusions:** Partial tonsillectomy does not seem to offer an immunological advantage over total tonsillectomy. The literature does not imply a significant negative impact of tonsillectomy on the humoral immune system.

**Keywords:** Humoral Immunity, Partial Vs, Total Tonsillectomy, Serum and Saliva Immunoglobulin

## 1. Background

The palatine tonsils are secondary lymphoid organs, important in sampling antigens directly from the epithelial surfaces. They produce antibodies locally and distally through their migrating B cells.

Obstructive tonsils became currently the most common cause of tonsillectomy in children. To decrease the postoperative discomfort, tonsillar reduction (also known as partial tonsillectomy, intracapsular tonsillectomy or tonsillotomy) was revived in 2002 by Koltai and gained the interest of both physicians and parents. The immunological benefit of this technique remains unknown (1).

We conducted this pilot study to look at the effect of partial tonsillectomy on serum immunoglobulins (Ig) A, G

and M, on salivary (S) IgA levels (short-term) and on the susceptibility to infections (long-term). The results were compared to those of total tonsillectomy. A systematic review of the English literature was undertaken regarding the effect of tonsillar surgery on the humoral immune system in children.

## 2. Objectives

The aim of this study was to compare the changes in serum and saliva immunoglobulin (Ig) levels after total vs. partial tonsillectomy and also to systematically review the literature regarding the changes in humoral immunity following tonsillar surgery.

### 3. Patients and Methods

#### 3.1. Patients

Children with obstructive tonsils were randomized to undergo either partial or total tonsillectomy after consent was obtained from the parents or legal guardians. The parents chose the procedure for their children after going through the details of both techniques. The study was approved by the institutional review board of the American University of Beirut. Children with a history of recurrent tonsillitis, immunodeficiency, chronic infections, or receiving immune-stimulants or suppressants were excluded. Blood and saliva samples were obtained immediately preoperatively and at the 1<sup>st</sup> follow-up visit, planned within 3 months postoperatively. The patients had a history of symptoms suggestive of upper airway obstruction for at least 3 months duration.

The patients were clinically reviewed at one year to check the frequency of febrile illness, the mean duration of missed school days, the frequency of visits to the doctor's office, the frequency of antibiotic uptake, any change in the severity or frequency of existing allergic rhinitis symptoms (or emergence of new ones), and the emergence of any chronic diseases.

#### 3.2. Surgery

##### 3.2.1. Microdebrider-Assisted Partial Tonsillectomy

With the patient under general anesthesia and using the microdebrider (XPS, Xomed, Medtronic, Jacksonville, FL) at a speed of 1500 rpm, each tonsil was shaved in layers from medial to lateral along the length of the tonsil. All tonsillar tissue protruding beyond the pillars was removed, leaving a smooth surface overlying the intact capsule. Hemostasis was achieved using suction-cautery at 17-20 Watts.

##### 3.2.2. Electrocautery-Assisted Total Tonsillectomy

Using the same positioning and exposure, dissection was performed in the plane separating the tonsillar capsule from the pharyngeal muscle using a combination of blunt dissection and electrocautery at a power of 13 - 15 Watts until the tonsil was completely removed with its capsule. Hemostasis was achieved using suction-cautery at 17-20 Watts.

#### 3.3. Samples

##### 3.3.1. Saliva

Saliva samples were collected by suction from the oral cavity intra-operatively before starting the surgery and by simple drooling on follow-up. The saliva was collected in sterile tubes and centrifuged at 3500 rpm for 23 minutes

and stored in micro-centrifuge tubes at -70°C. The SIgA concentration was measured using an indirect enzyme immunoassay kit (Salimetrics Inc, State College, PA).

Saliva samples were thawed completely, vortexed, and centrifuged at 3000 rpm for 15 minutes. Five microcentrifuge tubes were labeled 2 to 6, and 30  $\mu$ L of 1x SIgA diluent in tubes were pipetted in the tubes. A SIgA standard was diluted three times by adding 15  $\mu$ L of the 600 $\mu$ g/mL standard (tube 1) to tube 2. Fifteen  $\mu$ L were transferred from tube 2 to tube 3, and so on for tubes 4, 5, and 6. The final concentrations of standards for tubes 1 to 6 were respectively 600 $\mu$ g/mL, 200 $\mu$ g/mL, 66.7 $\mu$ g/mL, 22.2 $\mu$ g/mL, 7.4 $\mu$ g/mL, and 2.5 $\mu$ g/mL. Saliva samples were diluted five times by adding 100 $\mu$ L of 1x SSIgA diluent to 25  $\mu$ L of each saliva sample.

Five mL sterile tubes were labeled for each standard, control, unknown sample, and one tube for the zero value. Four mL of 1x SIgA diluent was added to each tube. And 10 $\mu$ L of standard, control, or unknown diluted saliva samples were added to the appropriate tube. Ten  $\mu$ L of 1x SIgA diluent was added to the zero tube.

The antibody-enzyme conjugate was diluted 1: 120 by adding 25  $\mu$ L of the conjugate to the 3 mL of 1x SIgA diluent. Fifty  $\mu$ L of the diluted antibody-enzyme conjugate was added to all tubes. The tubes were mixed by inversion and incubated for 90 minutes at room temperature. After incubation, the tubes were mixed again by inversion and 50  $\mu$ L of each tube was pipetted in the wells of the micro-titer plate in duplicates. Fifty  $\mu$ L of 1x SIgA diluent were added to two wells for the determination of the diluent optical density (OD).

The plates were covered with an adhesive plate sealer and incubated at room temperature with continual mixing for 90 minutes. The plates were then washed 6 times with 1x wash buffer. After each wash, the plates were thoroughly blotted on paper towels. Fifty  $\mu$ L of Tetramethylbenzidine solution was added to each well and mixed by tapping for 5 minutes. The plates were then incubated in the dark at room temperature for an additional 40 minutes.

Fifty  $\mu$ L of stop solution was then added and mixed by tapping until the wells turned yellow. The OD's of the wells were read on ELX- 800 plate reader (NIO- TEK instruments, VT, U.S.A) at 450 nm, within 10 minutes of adding stop solution. The average OD was computed for all duplicate wells. The average OD for the diluent OD wells was subtracted from the average OD of the zero, standards, controls and unknowns. The percent bound was calculated for all samples, and concentrations were determined from the standard curve of absorption versus concentration. The unknowns' concentrations were multiplied by five to account for the dilution. Results were reported in  $\mu$ g/mL.

### 3.3.2. Serum

Serum was collected by centrifuging patient blood at 3500 rpm for 10 minutes. Serum was transferred with a dropper and stored in a sterile tube at -20°C. Serum Ig G, M and A concentrations in pre and postsurgery samples were measured by radial immunodiffusion according to the manufacturer's protocol (Dade Behring, Marburg GmbH, Newark, USA).

The plates were opened and left for 5 minutes at room temperature. Five  $\mu\text{L}$  of serum from each patient was dispensed into the wells. The plates were covered and allowed to stand at room temperature. Forty-eight hours later, the diameter of the precipitin rings was measured with a ruler that is accurate to 0.1 mm. The concentrations corresponding to the diameters were calculated from the tabulation of reference values. The squares of the diameters of the precipitin rings were measured after 48 hours of incubation and concentrations in g/L were deduced from standard reference tabulations.

### 3.4. Statistical Analysis

Paired t-test was used to determine the significance of differences between pre- and post- tonsillectomy mean serum Ig and SSiGA concentrations of both partial and total tonsillectomy. P values less than 0.050 were regarded as significant.

### 3.5. Literature Review

A systematic review of the English literature was performed using Medline, Embase and Cochrane. We used the terms tonsillar reduction, tonsillotomy, intracapsular tonsillectomy, tonsillectomy, adenotonsillectomy, humoral immunity, immune system, immunity to look for pertinent studies. We included all articles that studied the humoral immunity whether alone or in combination with other aspects of the immune system (i.e. cellular immunity); however, only the humoral aspect of the paper was analyzed. We excluded duplicate publications, reviews and studies that did not include actual measurements of the humoral immune system (e.g. using only questionnaires).

## 4. Results

### 4.1. Pilot Study

Twenty six patients were enrolled; however, only 19 patients, aged 3 to 10 years (mean of 5.11 years, median 4 years) completed the study. The other 7 patients had only postoperative saliva samples available and thus were excluded from the study. There were no statistically significant changes in serum Ig levels after partial or total tonsillectomy (Table 1), except for IgM which significantly increased after partial tonsillectomy ( $P = 0.018$ ), mainly in

males ( $P = 0.040$ ), and in those aged 5 years and older ( $P = 0.022$ ).

There was a statistically nonsignificant decrease in the SSiGA level after both partial (172.35 to 111.54  $\mu\text{g}/\text{mL}$ ) and total (98.39 to 89.90  $\mu\text{g}/\text{mL}$ ) tonsillectomy (normal value: 17.1 - 93.1  $\mu\text{g}/\text{mL}$ ). The decrease was relatively greater after partial tonsillectomy. Postoperatively, the SSiGA level remained higher than normal limits in the partial while it became normal in the total tonsillectomy group.

At one year follow-up, there was a noticeable decrease in the susceptibility to infections as reflected by a significant decrease in frequency of febrile illness (67% decrease in partial, 71% in total), in frequency of visits to the doctor's office (86% decrease in partial, 79% in total), in frequency of antibiotics' intake (97% decrease in partial, 96% in total) (Figure 1).

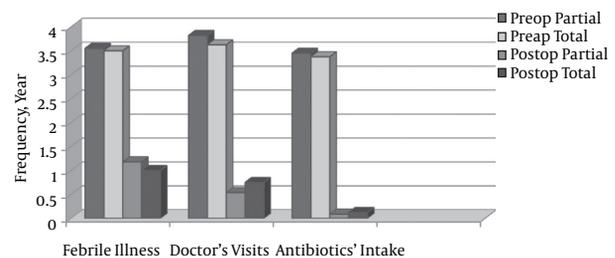


Figure 1. The Improvement in the Frequency of Febrile Illness and its Sequelae in Children Who Underwent Partial or Total Tonsillectomy

There was also significant drop in the duration of febrile illness (61% decrease in partial, 60% in total), and in frequency of absenting from school (96% decrease in partial, 93% in total) (Figure 2). No patient developed new allergies or a chronic disease.

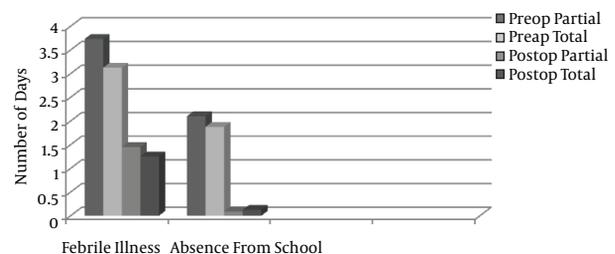


Figure 2. The Decrease in the Duration of Febrile Illness and its Sequelae in Both Groups

### 4.2. Systematic Literature Review

We could identify 30 studies that assessed the changes in the humoral immune system in patients undergoing

**Table 1.** Serum IgG, IgM and IgA levels Pre- and Post-Partial and Total Tonsillectomy (g/L)

Serum	Pre		Post		Pre - post		Normal Range <sup>a</sup>	P Value	
	PT	TT	PT	TT	PT	TT		PT	TT
IgG	11.273 ± 2.298	9.688 ± 1.624	11.427 ± 3.179	9.713 ± 1.744	-0.155	-0.025	7 - 16	0.834	0.959
IgM	1.317 ± 0.459	1.438 ± 0.350	1.632 ± 0.672	1.500 ± 0.389	-0.315	-0.063	0.4 - 2.30	0.018	0.351
IgA	1.487 ± 0.700	1.678 ± 0.489	1.604 ± 0.778	1.613 ± 0.461	-0.118	0.064	0.7 - 4	0.257	0.649

Abbreviations: PT, partial tonsillectomy; TT, total tonsillectomy.

<sup>a</sup>Normal range used in our laboratory.

tonsillectomy. The literature has focused mainly on total tonsillectomy and often mixed data regarding patients with tonsillitis and enlarged tonsils in the assessment of results. Four studies involving 406 patients showed a decrease in some elements of the humoral immunity or suspected a negative impact of tonsillectomy on the immune system (Table 2) (2-5); while 26 studies, including 1796 patients, showed no negative effect (Table 3) (6-31).

## 5. Discussion

The role of the palatine tonsils in the immune system and the immunological sequelae of tonsillectomy in children have long been a source of debate among physicians and a continuous concern for the parents.

No doubt that the tonsils have an important role in the immune defense mechanism of the upper aero-digestive tract. In fact, the memory B cells in the crypt epithelium play an important role in generating a rapid secondary immune response. They have a strong antigen presenting ability enabling them to activate memory T helper cells in the crypt epithelium rapidly (32).

Moreover, the tonsils are connected to the body immune system through trafficking of immune cells. The naive T and B cells are transported into the tonsils via the high endothelial venules present in the extrafollicular regions. While plasmablasts migrate from the tonsils via efferent lymphatic vessels, drain in cervical lymph nodes, join circulation and then disseminate preferentially to upper airway mucosa, regional exocrine glands including lacrimal and salivary glands and to a lesser extent to the gut mucosa (32).

However, does that mean that tonsillectomy is harmful to the immune system and tonsillar reduction is protective? In the present study, that was not demonstrated. In both types of surgeries, the mean serum Ig levels were within normal limits both pre- and postoperatively. The changes, except for IgM, were nonsignificant. Even the significant changes in IgM levels after partial tonsillectomy were within normal limits. The prominence of these significant changes among males, and in patients 5 years and older, is interesting and worth investigating in a larger

scale study, to disclose its significance. This most probably represent a kind of readjustment after surgery. We have compared our serum Ig levels to the normal range used in our laboratory and to published values stratified per age and sex.

The SSiGA levels have been shown to increase with age, yet not in a significantly incremental way. A study by Nagao et al. showed that there was no statistical difference among levels detected between the age of 1 and 6 years and similarly among levels detected between the age of 7 and 12 years (33). Thus, the values could be grouped into 1 - 6 and 7 - 12 categories. Our mean age in both groups fell in the 1st range, where comparison was done. The high mean values encountered in our study reflected the active role of tonsils in producing SSiGA. However, the normalization of preoperatively low SSiGA values (in some patients) after operating on the tonsils could not be explained (Table 4).

Both partial and total tonsillectomies were effective in decreasing the frequency of febrile illness, and eventually the rate of visits to the doctor's office or the need for antibiotics' intake, indicating a significant improvement in the children's quality of life.

The reviewed literature is controversial about the effect of tonsillectomy on the humoral immune system. Of the 30 studies identified to have assessed the humoral immunity, only 4 showed a decrease in some elements of the humoral immune system or suspected a negative impact of tonsillectomy on it. One of the first studies dates back to 1971, when Ogra (2) noticed that the production of IgA in response to administering live attenuated polio vaccine in the nasopharynx was decreased in tonsillectomized patients, raising concerns regarding effect of tonsillectomy on the humoral immune system. Six years later, Ostergaard PA (3) looked at the serum Ig's and SiGA 2.5 years after tonsillectomy. Though there was no significant change in SiGA and serum IgE, the serum IgA, G and M decreased significantly. However, this was not translated clinically in most of the patients in terms of recurrent infections. There was no definite conclusion regarding the real reason behind that drop in serum Ig's.

In 1982, D'Amelio et al. (4) found that the serum IgA was significantly lower in tonsillectomized patients compared

**Table 2.** Studies that Showed or Suspected a Negative Impact of Tonsillectomy on the Humoral Immune System

Authors/Year	No/Age	Studied Immunity Elements	Control/Time of Testing	Findings	Conclusion
1) Ogra P L, 1971 (2)	40 (3 - 11y)	Serum and NP Ig's to polio virus	-Preop levels -24 controls * Up to 7 months postop	Preop: IgA was present in NP; Postop: IgG appeared in NP in 50% only for 2 months. IgA in NP declined 3 - 4 folds; Controls: have 2-4 folds higher NP Ig response than operated ones	Tonsillectomy impairs development and maintenance of Ig's in NP against polio virus.
2) Ostergaard PA, 1977 (3)	27 (6 - 11y)	-Serum IgA, IgG, IgM, IgE, -SIgA	-Preop levels, -27 controls, *2.5 y postop	Clinically 5/27 continued to have recurrent infections; Preop: Serum IgA was low; Postop: Serum IgA further decreased. Ig's G and M decreased and became lower than controls. -No significant change in SIgA or serum IgE	It is unclear whether the drop in Ig's G and M is due to removal of chronically infected organs or to removal of important immunological tissue.
3) D'Amelio R. et al. 1982 (4)	274 (16 - 24y)	-Serum IgA, -SIgA	-726 controls	Preop, data not available; Postop, serum IgA levels were significantly lower in tonsillectomized subjects. SIgA levels were non significantly different	The role of tonsillectomy in IgA deficiency is still unclear. Tonsillectomy should be performed only when precise indications exist, based on strict clinical criteria
4) Cantani A, et al. 1986 (5)	65 (2 - 11y)	-Serum Ig's M,A,G, -SIgA	-Preop Levels *1 month; postop * 4 months postop	-Preop: normal serum Ig's and SIgA levels; -Postop: significant; drop in levels after 1 and 4 months	The palatine tonsils are important in the synthesis of Ig's. Serum Ig's and SIgA levels should be determined in all children before and after surgery, to avoid any possible immunologic complication.

Abbreviations: Ig, immunoglobulin; NP, nasopharynx; Preop, preoperative; Postop, postoperative; S, salivary.

to controls. However, there were no preoperative values to compare with. That deficiency was well recognized by the authors admitting that no definite conclusions regarding serum IgA deficiency in tonsillectomized subjects may be drawn. It is worth noting that the patients were adolescent and young adults with age ranging from 16 to 24 years.

On the other hand, Cantani et al. (5) suggested to perform tonsillectomy only when strict clinical indications are accompanied by normal results of serum Ig's and SIgA levels. That was based on the observation that tonsillectomy does significantly decrease the serum Ig and SIgA levels, compared to preoperative values, 1 - 4 months postoperatively. However, these results reflect early changes in the humoral immunity and longer follow-up is needed to show if that negative effect is long standing or just transient. It is not clear if the postoperative values were lower than the age matched normal values in the lab.

Our results agree with those of the 26 studies that showed no negative influence of tonsillectomy on the immune system. These studies were more comprehensive in

terms of the variety of immune factors studied compared to the above four mentioned ones. It is worth noting that no study beyond 1986 found a negative impact of tonsillectomy on the humoral immune system. Could the type of lab technology play a role in the various studies' findings? It is a question worth answering by the experts in lab testing procedures.

Looking at all the reviewed studies, we suggest the following for future studies on this subject:

- To stratify patients according to age group < 5 years old vs. > 5 years old

- To compare both the preoperative and postoperative levels to a control group and specify if they are normal or not.

- Not to mix tonsillitis (representing a continuous antigenic stimulus) with tonsillar hypertrophy cases.

### 5.1. Conclusion

Partial tonsillectomy does not seem to offer an immunological advantage over total tonsillectomy. The ob-

tained results are preliminary and larger studies and longer follow-ups of the Ig's and SIgA levels are needed to confirm these findings. The literature does not imply consistently a negative effect of tonsillectomy on the humoral immune system. There is no current evidence that the observed drop in some elements of the humoral immunity is affecting the clinical course of the affected patients.

## Footnotes

**Conflicts of Interest** The authors declare that no conflict of interest exists.

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**Table 3.** Studies That Found no Negative Effect on the Humoral Immune System (Including the Current Study)

Authors/Year	No/Age	Studied Immunity Elements	Control/Time of Testing	Findings	Conclusion
1) Veltri RW et al. 1972	17 (2 - 10y)	-Serum Ig's G, M, D,A, -SIgA, -Ig's to respiratory viruses	-Preop levels, *1, 3, 9 to 12 months postop	Preop: Ig's G and A were above normal; Postop: IgG dropped to normal level. No change in Ig's A,M,D. SIgA was not affected.	Tonsillectomy does not modify host's systemic immunological competence.
2) Donovan R, and Soothill J F; 1973	36, (3 - 12y)	-Serum Ig's G,A, M,E-SIg's, -ASO titer	-Preop levels, -20 controls, *6 months postop	Preop: low serum IgA level. Normal Ig's G,M,E levels; Normal SIg's; Postop: only 4 patients were tested. Serum IgA remained low	The low IgA was not due to tonsillectomy but to a primary minor immune deficiency in IgA
3) Gogoi D et al. 1979	80, (5 - 14y)	-Serum Ig's G,M, A	-Preop levels, -20 controls, *3 months postop (10 pts)	Preop: Serum Ig's normal; Postop: No significant variation in serum Ig's G,A,M levels.	No significant variations in Ig's levels
4) Virolainen E et al. 1979	8 (10y), 9 (mean age 20y)	- serum Ig's A,G,M, - NBT test, C3, C4 and Ab's to polio, diphtheria, tetanus and pertussis. (only in adults)	-Preop levels (Ped), *1 month (Ped), *10 yrs (adults)postop	Preop: Ig's were normal; Postop: no changes in Ig's. Ab's titer against polio, diphtheria, tetanus and pertussis were normal.	All the parameters studied were found to be normal.
5) El-Ashmawy S et al. 1980	10, (5 - 14)	Serum Ig's A,G,M,D	-Preop-10 controls, *2 months postop	Preop: significantly elevated IgG and A; Postop: Significant decrease in IgG and A to normal	Tonsillectomy does not seem to compromise immunological integrity
6) Yamauchi S et al. 1981	54, (4 - 55y)	Serum IgG, IgA, IgM, Serum humoral factors	-Preop values-20 controls, -postop (un-specified timing)	-Preop: Ig's and humoral factors lower in patients <8 years old;-Postop: Ig and humoral factors lower than normal in patients <8 years old	No negative effect in general; Patients < 8years old have low Ig's and humoral factors to start with and these remained low postop.Humoral factors= alpha2 macroglobulin, alpha1 acid glycoprotein, ceruloplasmin, haptoglobin, transferrin, alpha1 antitrypsin, G3c
7) Lal H., et al. 1984	40, (5 - 15 y)	-Serum Ig's A,G,M, -ESR level	-Preop levels, -40 controls*1 month postop	- Preop: level of Ig's and ESR significantly higher than the control group;-Postop: Decrease in serum IgG (but to control levels). nonsignificant decrease in Ig's A and M level. ESR dropped to control level.	Tonsillectomy does not adversely affect the humoral immune system.
8) Friday G. A, et al; 1992	268, (1.5 - 16 y)	Serum Ig's A,G,M	-Preop levels, -152 controls, *7 - 30 months,postop	Preop: normal levels; Postop: decrease in serum IgG levels compared to controls. The higher the level of Ig's preop., the greater the decrease in level; No correlation between the changes in Ig's level and the frequency of throat infections on follow-up.	The findings argue against the notion that post-tonsillectomy reductions in serum Ig's levels might heighten the risk of subsequent throat infection.

9) M. Lenander-Lumikari et al;1992	53, (5 - 8.5 y)	-Slg's A,G,M; salivary lactoferrin peroxidase, myelo-peroxidase -Ab's against viral antigens and against streptococcus mutans	-69 controls*3-4 y postop	Postop: higher levels of Slg's and higher levels of lactoferrin and myeloperoxidase.- Higher levels of Ab's against viruses-No difference in anti Streptococcus mutans Ab's	- Tonsillectomy does not affect the humoral immune response of individuals- Salivary aerobic bacteria did not differ between the tonsillectomized and the control group
10) Sainz et al; 1992	30 (5 - 10 y)	-Serum Ig's A,G,M,E; complement factors 3 and 4-synthesis in vitro of Ig's G,M by lymphocyte stimulated with pokeweed mitogen	-Preop levels*1 month postop	-Postop: significant decrease in level of serum Ig's (within normal range) with the exception of IgE-no difference in complement levels -In vitro synthesis of Ig's G,M increased after surgery enhanced lymphocytic activity for immunological response due to their release from immune-suppression	-Complement level did not change postop-Since IgE did not change postop means that no allergic substrate in the tonsils is involved in tonsillitis -Tonsillectomy have no counterproductive effect on the immune system -It seems to improve the immune response, since it appears to unblock the suppression to which the immune system was subject to.
11) Bock A et al; 1994	160, (4 - 8 y)	-Ig's M,A,G,E	-302 controls, *0.5-11 y (mean 6.6 y) postop	Postop: lower IgA levels, but the complement system was not altered. -Incidence of infections of the upper respiratory tract was not increased	Tonsillectomy may lead to certain changes in the humoral immune systems that are clinically insignificant
12) Del Rio-Navarro BE et al; 1995	33; (3 - 13 y)	-Ig's A,G,M, -SlgA	-Preop levels, *1-4, 5-12, and after 12 weeks postop	-Postop: SlgA significantly increased, Ig's A,G significantly decreased (within normal range), no changes in IgM	-The SlgA increase may be a compensatory mechanism to the lack of tonsils.-The changes post tonsillectomy are clinically insignificant
13) Kirstila V et al; 1996	25, (15 - 34 y) mean 24 y	-Slg's A,G,M- Anti-Strepto-coccus mutans Slg's - Anti-EBV,CMV,adenovirus Slg's A,G - S lysozyme, lactoferrin, peroxidase systems, agglutinins	-Preop levels *1 and 6 months postop	-At 1 month: Slg's G,A,M levels decreased, but only significantly for IgM. -At 6 months: SlgA returned to normal, SlgG increased but SlgM remained low - S non-immune antimicrobial proteins slightly decreased except for lactoferrin-No change in antiviral Slg's except for SlgG against EBV which decreased significantly-No change of anti Streptococcus mutans Slg's A and M but a significant decrease in specific SlgG at 6 months	-Tonsillectomy does not affect the non-immune salivary defense against oral antigens, and most of the immune factors (Ig's), except for the IgM and specific anti Streptococcus mutans and anti-EBV IgG. This may represent a reduction in the preop antigenic stimulation.
14) Jung KY et al. 1996	66, (<4->19 y)	-IgA-SlgA	- Preop levels-60 controls *1month post op	Preop: IgA higher than controls in age<10 y; Postop: IgA and SlgA decreased to control levels	No significant changes in the local immune system occur after tonsillectomy
15) Jurkiewicz D et al; 1997	30, (3-14 y)	-Ig's A,G, M	-Preop levels; *3months postop	Preop: significantly high IgA,M,G levels compared to controls; Postop: normalization of levels	No persistent negative effect on the immune system

<b>16) Childers NK et al; 2001</b>	25, (4.4 - 12.8 y)	-SIgA, - Ag-specific Ig in saliva and serum	-25 controls, *6-14 months postop	-The whole saliva total and specific SIgA and the specific serum IgA or IgG activities were not significantly different from controls.-There was significantly higher parotid SIgA and IgA specific/total activity post-tonsillectomy than controls.	There is an association between the removal of tonsils and increased levels of specific SIgA activity in saliva within the first year after tonsillectomy.This may reflect an increased exposure to antigens or an activation of a compensatory mechanism
<b>17) Zielnik-Jurkiewicz B and Jurkiewicz D; 2002</b>	80, (3 - 14 y)	-Ig's A,M,G	-Preop levels-40 controls *1 and 6 months postop	Preop: statistically significant higher levels of Ig's A,M,G compared to controls; Postop: -at 1month: significant decrease in Ig's level -at 6months: significant increase in Ig's to a level similar to control group	There is significant changes in humoral immune components post-tonsillectomy which normalize after 6 months, knowing that these were abnormally high preop
<b>18) Ikinciogullari A et al; 2002</b>	15, (4 - 10 y)	-Serum Ig's G,A, M	-Preop levels-15 controls *4-6 weeks postop	Preop: A significantly high IgA level compared to controls Postop: Ig's G,A,M levels in the normal range.	Tonsillectomy results in changes that may indicate a compensatory response of the developing immune system to the removal of lymphoid tissue in the setting of chronic antigenic stimulation
<b>19) Kaygusuz I et al; 2003</b>	37, (5 - 9 y)	-Ig's G,M,A -C3 and C4	-Preop levels-35 controls *1month postop	Preop: Ig's G,A,M; C3 and C4; were higher than controls. Postop: significant decrease of Ig's; and C3 and C4 to control levels.	The humoral immune system is stimulated in patients with tonsillitis. Tonsillectomy removes this stimulus without negatively affecting the patient's immune functions.
<b>20) van den Akker et al; 2006</b>	63, (2 - 8 y)	-Ig's A,G,M	-Preop levels-60 controls *1 year postop	Preop: high serum Ig's levels; Postop: IgG decreased to normal levels; Ig's A,M decreased but to levels higher than normal	IgA showed a decrease but rose to control levels in cases of frequent URIs. This indicates that the remaining mucosa-associated lymphoid tissue can compensate for the absence of tonsils
<b>21) Baradaranfar MH et al; 2007</b>	30, (4 - 10 y)	-Ig's M,G	-Preop levels-30 controls-6months postop	Preop: normal levels; Postop: significant decrease of IgG postop (but still within normal)	No negative effect on immunity
<b>22) Kaygusuz I et al; 2009</b>	20, (10 - 14 y)	-Ig's G,M,A, -C3 and C4	-20 controls *1 month and 54 months postop	Postop: no significant differences between the short-term and long-term levels of Ig's and C4 levels - decrease in C3 value compared to its early-stage value but not different from control level.	Tonsillectomy does not compromise the humoral immunity of children
<b>23) Nasrin M et al; 2012</b>	70; (up to 18y)	Ig's G,M,A	-Preop levels-30 controls*1 and 3 months postop	Preop: no difference from controls; Postop: no significant change at 1 month; Sign decrease in IgG at 3 months compared to preop and controls levels (but still within normal range)	Humoral immune system was not significantly altered after tonsillectomy

<b>24) Santos FP et al; 2013</b>	29, (2 - 8 y)	-Ig's A,M,G	-Preop levels, *1-2 and 12-14 months postop	Postop: significant decrease in Ig's A,G at 12-14 months (but within normal range)	Humoral immune system was not affected by tonsillectomy
<b>25) Pidelaserra Marti et al; 2014</b>	45, (3 - 17 y)	-Ig's G,M,A	-preop levels, *up to 12 months postop	Postop: no change in levels- response to influenza vaccine was not affected	Tonsillectomy does not compromise systemic humoral immunity nor the specific immunoglobulin response to influenza vaccination.
<b>26) Dai et al; 2014</b>	57	-Ig's G,M,A	-Preop levels *1 and 3 months postop	Postop: Ig's levels in the tonsillectomy group significantly decreased at 1 month, but recovered at 3 months Nonsignificant decrease in levels in the partial tonsillectomy group	Partial tonsillectomy by plasma-mediated temperature-controlled radiofrequency ablation did not impact on the humoral immunity of children.
<b>27) Bitar et al</b>	19, (3 - 10 y)	-Ig's G,M,A -SIgA	-Preop levels * 3 months postop	-No statistically significant changes noted in serum Ig's level, except for IgM which increased after partial tonsillectomy, mainly in males and in those aged 5 years and older -There was statistically nonsignificant decrease in SIgA level -There was noticeable decrease in susceptibility to infections as reported by caregivers.	The effect of both partial and total tonsillectomy on Ig's level and rate of infections seems reassuring. The noted changes may represent a kind of immunological readjustment after the surgery.

Abbreviations: DNBC, dinitrochlorobenzene; Preop, preoperative; Postop, postoperative; Ig, immunoglobulin; S, salivary; Ab, antibody; Ped, pediatrics; WBC, white cell count; PPD, purified protein derivative.

**Table 4.** Significant Individual Variations in SSIGa ( $\mu\text{g/mL}$ ) Among Patients<sup>a</sup>

Preoperative/Partial	Postoperative/Partial	Preoperative/Total	Postoperative/Total
205.848	49.8	111.806	87.14
214.397	190.727	413.222	158.813
188.125	66.889	64.221	115.858
43.853	17.51	158.813	102.544
312.383	415.329	5.5 <sup>b</sup>	70.47
639.97	53.748	15.11 <sup>b</sup>	46.33
128.81	124.59	8.38 <sup>b</sup>	48.16
16.95 <sup>b</sup>	45.34	10.07 <sup>b</sup>	89.85
11.42 <sup>b</sup>	91.46		
122.86	64.12		
11.25 <sup>b</sup>	107.42		

<sup>a</sup>Normal Value: 17.1 - 93.1  $\mu\text{g/mL}$ .

<sup>b</sup>Abnormally low.