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Interleukin 8 in Children with Obstructive Sleep Apnea before and after Adenotonsillectomy

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ABSTRACT

Background: A reduction in blood oxygen levels and periodic interruptions in breathing during sleep are hallmarks of obstructive sleep apnea (OSA).

Objectives: to determine the amount of serum IL-8 in children diagnosed with OSA both before & after undergoing adenotonsillectomy.

Patients and methods: Prospective randomized single-arm interventional trial. The research was conducted in the ENT Department of Suez Canal University Hospital, Ismailia City, Egypt. Children experiencing OSA and chronic intermittent hypoxia (CIH) signs during sleep. T & A was done on children as a matter of choice. Children's ages varied from three to twelve years old.

Results: We found that there was significant variation among preoperative & postoperative IL-8. There was no significant distinction among preoperative & postoperative O_2 levels ($p = 0.069$), with the mean preoperative O_2 level being 98.27% and the mean postoperative O_2 level being 98.77%. The preoperative oxygen desaturation index (ODI) was significantly distinct from the postoperative ODI. The preoperative ODI had a mean value of 7.77, whereas the postoperative ODI had a mean value of 2.90.

Conclusion: The levels of IL-8 in the children who had OSA were elevated. Children who had OSA showed a significant reduction in their IL-8 levels following adenotonsillectomy.

Keywords: IL-8, Adenotonsillectomy, Obstructive sleep apnea.

INTRODUCTION

The occurrence of recurrent episodes of interrupted breathing while sleeping as well as recurrent reductions in blood oxygen saturation are the factors that define OSA [(1)].

Obstructive sleep disordered breathing (SDB) is extremely prevalent among children. Peak incidence occurs among the ages of two and eight, probably due to the proportional size of lymphoid tissue to airway diameter. The frequency of primary snoring in adolescents has been noticed to range among four percent and twelve percent [(2)]. Severe OSA if left untreated can have serious consequences for children's health and academic performance [(3)].

As an autocrine growth factor for colon carcinoma cell lines, or by encouraging cell division and may be migration via metalloproteinase cleavage, IL-8 has also been hypothesized to have a role in colorectal cancer. It has also been determined that IL-8 induces expression of transmembrane transporters, which contributes to the chemoresistance of malignant pleural mesothelioma [(4, 5)].

The pathology of cystic fibrosis has also been related to IL-8. Neutrophils can be recruited and steered toward the lung epithelium thanks to IL-8's role as a signaling molecule. A variety of pro-inflammatory chemicals and proteases are released by these recruited neutrophils within the airways as a result of their overstimulation and malfunction, further damaging lung tissue [(6, 7)]. Due to elevated IL-8 serum concentrations in severe COVID-19 people, IL-8 may be a biomarker for illness treatment and prognosis [(8)].

Intercellular adhesion molecule 1 (ICAM-1) and IL-8 are examples of proinflammatory mediators that contribute to this increased adherence by activating nuclear transcription factor-KB. It has been shown that systemic ICAM-1 plays a crucial role in leukocyte migration to the inflamed region [(9)].

The study aimed to evaluate serum IL-8 level before and after adenotonsillectomy in children with OSA.

PARTICIPANTS AND METHODS

Study design: Randomized single arm pre-post prospective interventional research.

Study population: Children with obstructive sleep apnea who were individuals at the ENT Clinic at Suez Canal University Hospital.

Inclusion criteria:

Children who displayed signs of OSA and CIH that are connected to sleep. Children will be given the option to undergo T & A. Age ranged from three to twelve years old.

Exclusion criteria:

Acute tonsillitis in children defined as a temperature above 38.3 degrees Celsius, presence of cervical lymphadenopathy (tender or swollen > 2 centimeters lymph nodes), tonsillar or pharyngeal effusion, and a positive culture for group A -hemolytic streptococcus. Children who had medical history including cardiovascular, neurological, allergy, craniofacial and immune system, or genetic

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abnormalities. Children who suffered from diseases affect IL-8 level as cystic fibrosis, acute pyelonephritis, nosocomial bacterial infections, vesicoureteral reflux, rheumatoid arthritis, cancer, obesity, otitis media, COVID-19 patients with severe diseases and Hepatitis C. Children prescribed on drugs affect IL-8 level as benzodiazepines and dexamethasone. Children receiving diet affect IL-8 level as glutamine supplementation.

Each of the participants underwent the following: Full history including personal history (Name, gender, age and address). Current illness history (Disease onset, course, & duration). The therapy and its administration time.

Medical examination:

Age, weight, height, & gender were recorded for clinical purposes. The body mass index was determined by dividing the respondent's kilogram weight by their square meter height. For this research, we employed a nocturnal pulse oximetry study (Choice MMed) (48-72 hours preoperatively and 3-4 weeks postoperatively) to count the number of 4% decreases in saturation from baseline and to identify the nadir saturation (nSAT). A questionnaire was given to parents to collect demographic and clinical information, and they were shown how to perform oximetry testing correctly. Our sleep researchers gave the oximeter to the parents, who brought it home and completed the study before sending it back to us.

Data management and statistical analysis

SPSS statistics version 25 (IBM Corporation, Armonk, NY, USA) was utilized for all data manipulation and analysis. Microsoft Excel was employed to generate all graphs. For continuous variables, measures of central tendency such as mean, SD, and range were determined mathematically.

For the purpose of describing categorical variables, we utilized both frequency and percentage descriptions.

The Kolmogorov-Smirnov test was applied in order to investigate how consistently distributed the variables were. Because the continuous variables did not follow a normal distribution, we used the Mann-Whitney test as well as the Kruskall-Wallis test. The application of Spearman's rank correlation allowed for the testing of the correlation among continuous variables. A p-value ≤ 0.05 was taken into consideration to be statistically significant.

Ethical considerations:

Approval from Research Ethics Committee (REC) of faculty of Medicine Suez Canal University was obtained before starting field work. Administrative approval was obtained from the dean of the faculty of Medicine. An Informed consent was obtained from children caregivers/guardians before taking any data or doing any physical examination. All the data were strictly confidential (for research purpose only). All participant's guardians were informed about the results of the research.

Each individual was permitted to withdraw from the research at any time, without explanation, and with no impact on their treatment plan. Individuals were given the researcher's phone number and all potential communication channels so they could return at any time for clarification. There was no conflict of interest in the trail. The study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Our research participants had an average age of 7.67 (3-12) years, an average weight of 23.68 (15-31) kilograms, an average height of 114.79 (93-131) cm and a mean body mass index of 18 (16-28) kilogram/m^2. The majority of our research cases (sixty percent) were females, while only (forty percent) were males (Table 1 and figure 1).

Table (1): Demographic characteristics of the examined sample

All cases		**Mean & SD**	**Median**	**Range**	**IQR**
Age (years)		7.67 ± 2.523	7.50	3.00, 12.00	5.75, 10.00
Weight (kg)		23.68 ± 4.397	22.75	15.00, 31.00	20.75, 26.50
Height (cm)		114.79 ± 8.690	114.50	93.00, 131.00	109.75, 121.00
BMI (kg/m^2)		18.00 ± 2.924	17.00	16.00, 28.00	16.00, 18.50
Gender	**Male**	40.0% (12)			
	Female	60.0% (18)			

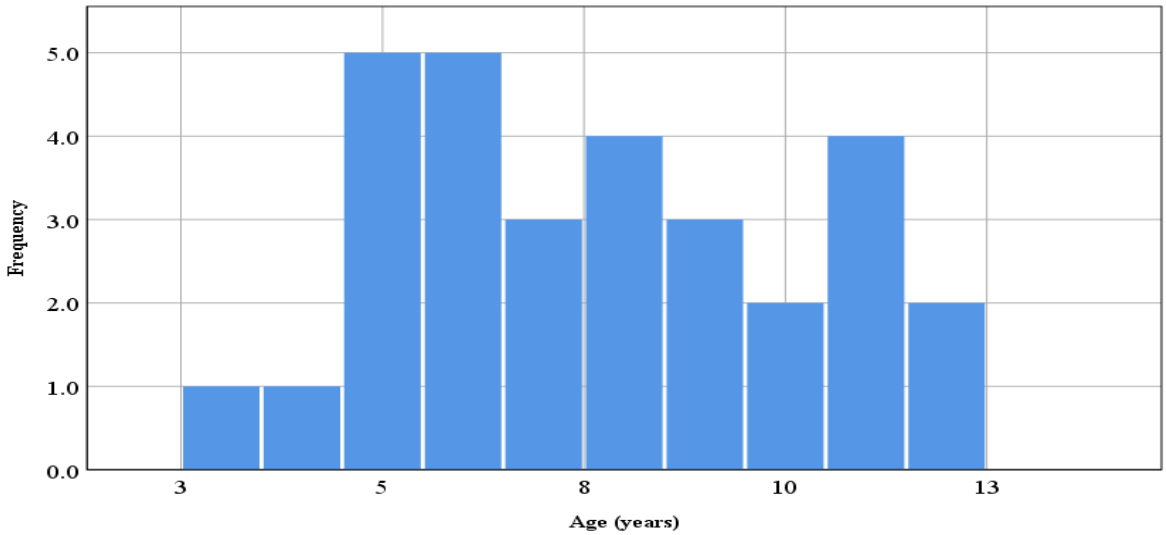


Figure (1): Age distribution in the current study.

Table (2) showed the duration of complaint and relevant medical history of the studied sample, the mean period of complaint was 2.93 (1-5) months.

Table (2): Duration of complaint of the examined sample

All participants (n= 30)	Mean ± SD
Duration of complaint (months)	2.93 ± 1.143

The mean preoperative IL-8 was 237.55 (72.00 - 420.20) p/ml, while the mean postoperative IL-8 was 207.98 (63.40 - 371.60) p/ml. There was significant variation among preoperative & postoperative IL-8 (Table 3).

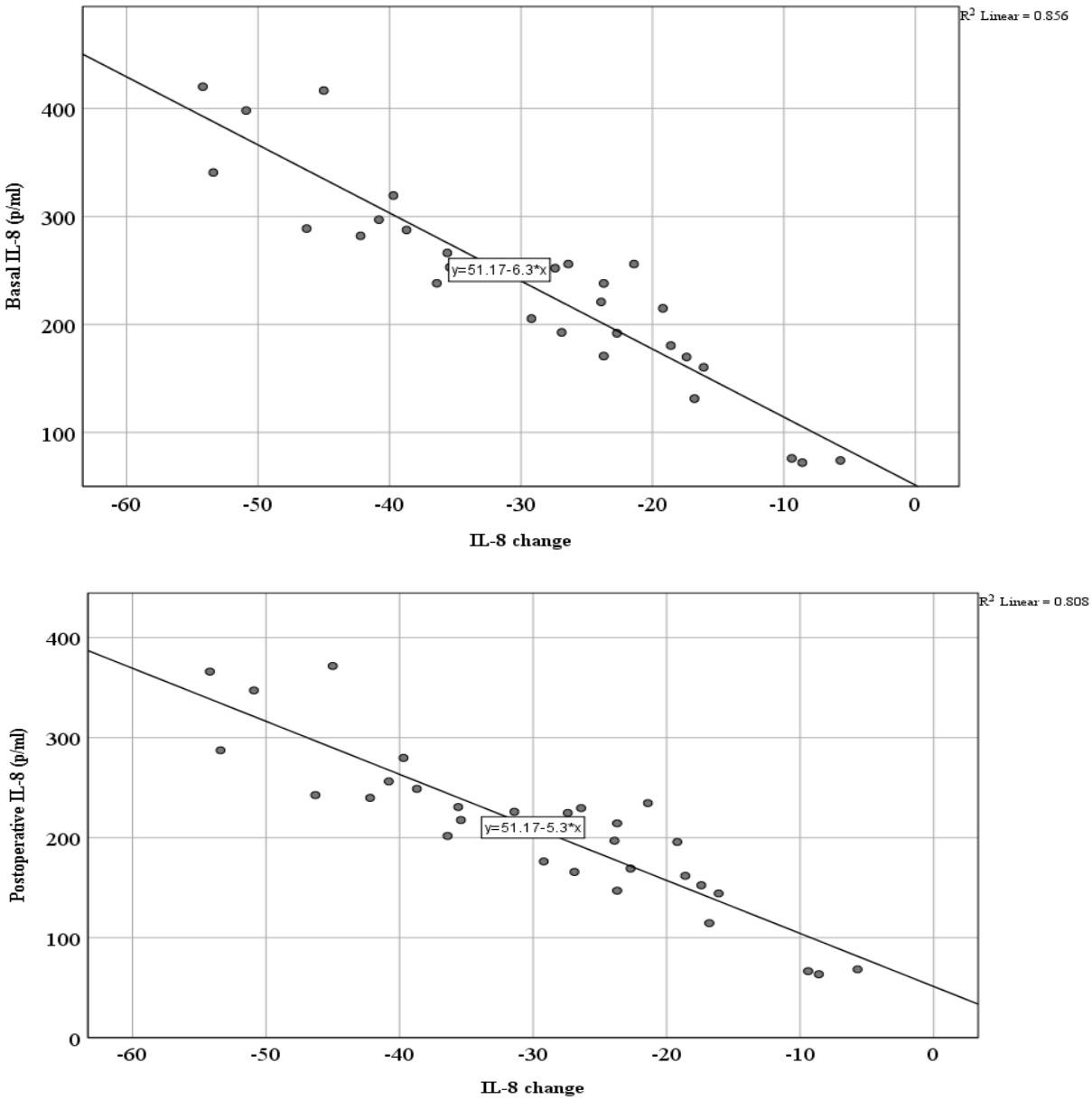
Table (3): Pre-operative & post-operative IL-8 of the examined sample

All cases		Mean ± SD	P
IL-8 (p/ml)	Pre-operative	237.55 ± 9.460	< 0.001
	Post- operative	207.98 ± 8.337	

Table (4) showed that the mean O_2 desaturation index was 7.77 (3.00 - 19.00%), while the mean postoperative ODI was 2.90 (1.00 - 8.00). There was significant distinction among preoperative and postoperative ODI.

Table (4): Pre-and post-operative samples of oxygen saturation & desaturation index

All cases		Median	Range	IQR	P
O2 (%)	**Pre-operative**	98.00	96.00, 100.0	98.0, 99.0	0.069
	Post-operative	99.00	97.00, 100.0	98.00, 100.0	
ODI	**Pre-operative**	7.00	3.00, 19.00	5.00, 9.00	**< 0.001**
	Post-operative	2.00	1.00, 8.00	1.00, 4.00	



Figures (2 & 3): Correlation among IL-8 change across study with IL-8 (p/ml) levels both before and after surgery.

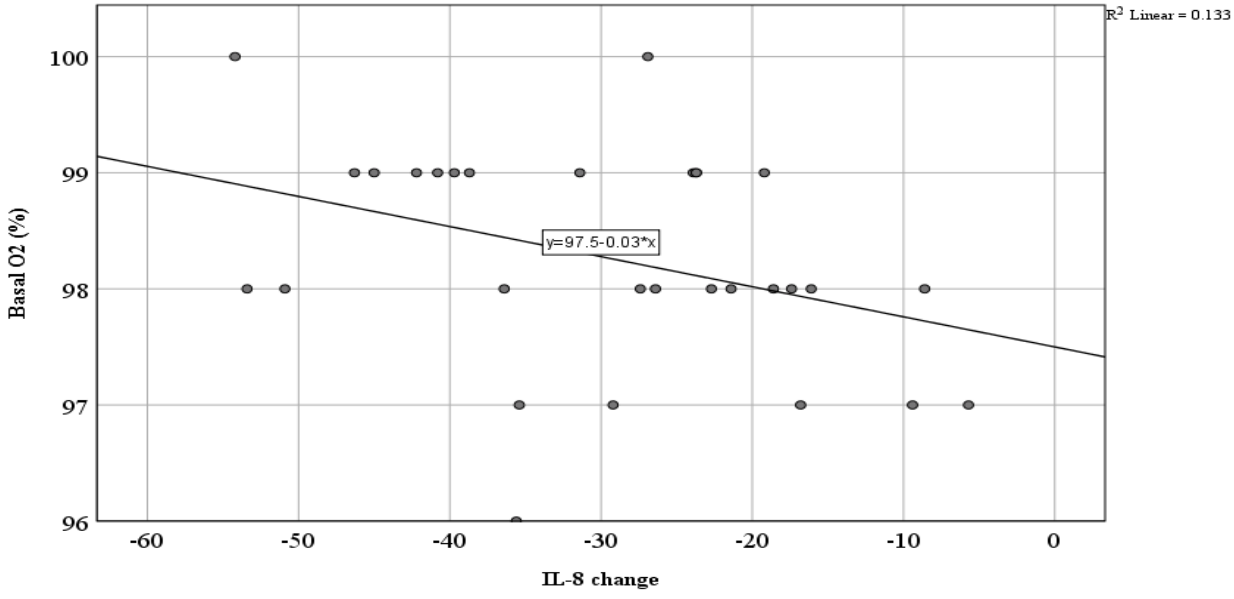


Figure (4): Correlation among IL-8 change across research with Preoperative O2 (%) in the sample.

Pre-operative IL-8, post-operative IL-8, as well as pre-operative O_2 (%) were determined to have a negative correlation with IL-8 change across this research (Table 5 and figures 2, 3 & 4).

Table (5): Correlation among IL-8 change and other sample variables.

All cases	Correlation coefficient	P
1Age (yrs)	-0.247	0.189
Weight (kilogram)	-0.170	0.370
Height (centimeters)	-0.014	0.940
Body mass index (kilograms per square)	-0.111	0.559
Duration of complaint (months)	-0.080	0.673
Pre-operative sleep time (min)	-0.101	0.595
Post-operative sleep time (min)	-0.128	0.501
Pre-operative IL-8 (p/ml)	-0.925	< **0.001**
Post-operative IL-8	-0.899	< **0.001**
Pre-operative O2 (%)	-0.413	**0.023**
Post-operative O2	0.132	0.485
Pre-operative ODI	-0.202	0.284
Post-operative ODI	-0.259	0.167
P is significant when below 0.05.		

DISCUSSION

We found that the average age of our research individuals was 7.67 (range, 3-12) years. Average weight was 23.68 (range, 15-31) kilogram. Average height was 114.79 (range, 93-131) centimeters and their average body mass index was 18 (range, 16-28) Kg/m^2. 60% of our participants were females and 40% were males. The average complaint duration was 2.93 months (1-5 months).

The chemokine interleukin-8 is essential for both the host immune response and for the process of angiogenesis [(10)]**.** Increases in inflammatory markers such as IL-8 have been observed in adults with OSA. Recent investigations have also shown that childhood OSA is linked to increased inflammatory mediators [(11)]**.**

Metinko *et al.* [(12)] found that anoxic preconditioning and oxidative stress boosted IL-8 production in monocytes. OSA has been identified to raise systemic inflammatory indicators such as IL-6 and IL-8 levels, as well as to generate reciprocal alterations in anti-atherogenic cytokines such as IL-10 in this context [(13)]. In **Ohga *et al.*** [(14)] research, untreated OSA cases had substantially higher circulating IL-8 levels in comparison with controls. **Andersson *et al.*** [(15)] also revealed that human tonsils with chronic infection produce more of nineteen distinct cytokines (which involves IL-4, IL-1ß, IL-8, IL-6 and TNF-α).

Nevertheless, **Tam *et al.*** [(16)] was unable to show that children with OSA had significantly higher levels of IL-8 after accounting for sex, age & BMI. The average age of OSA patients in this study was lower than in our own. The difference amongst **Tam *et al.*** [(16)] and our study can be explained by the fact that our individuals were younger and, as a result, experienced a shorter duration of disease and, by extension, a shorter duration of the putative pro-inflammatory period.

After adenotonsillectomy, the level of IL-8 was shown to be substantially reduced in our research. In **Ke *et al.*** [(17)] study, IL-8 improved substantially after T & A. However, the peripheral blood mononuclear cells samples from children with severe sleep-related CIH were cultured under normoxic conditions, which may have elevated their IL-8 production. Therefore, CIH preconditioned the circulating mononuclear cells, while the molecular processes linking sleep-related CIH and IL-8 production remain unclear. The stimuli leading to tonsillar hypertrophy were another probable cause for the increased IL-8 production capability.

We found no significant variation in O_2 levels among before and after surgery. Nevertheless, the ODI before and after surgery were substantially distinct. In **Mitchell** [(18)] research, by comparing cardiorespiratory measurements and sleep architecture prior to and after adenotonsillectomy for pediatric OSA, significant changes in mean O_2 saturation & the central apnea index were found. However, there were no statistically significant shifts in either the average amount of time spent sleeping or how much of that time was spent in REM sleep [(18)]**. Stewart *et al.*** [(19)] revealed that after undergoing adenotonsillectomy, a sample of children aged 6 to 12 showed considerable improvements in quality-of-life indices and sleep research characteristics. The mean apnea-hypopnea index (AHI) preoperatively was 4.8 (1.0 to 75.8) in a group of sixteen children with both pre- and post-operative PSG data, and it decreased to 3.16 after surgery. Postoperatively, the nadir oxygen saturation level was higher than the preoperative level by 9%. Only 9 out of 17 individuals with OSA were considered cured.

CONCLUSIONS

The amount of IL-8 rises in children who suffer from OSA. After adenotonsillectomy, the amount of IL-8 in children with OSA was significantly reduced.

DECLARATIONS

- **Consent for publication:** All authors agreed to submit the work.
- **Availability of data and material:** Available
- **Competing interests:** None
- **Funding:** No fund
- **Conflicts of interest:** No conflicts of interest.

REFERENCES

1. **Abijay C, Tomkies A, Rayasam S *et al.* (2022):** Children with Down syndrome and obstructive sleep apnea: outcomes after tonsillectomy. Otolaryngol Head Neck Surg., 166 (3): 557-564. doi: 10.1177/01945998211023102.
2. **Lam D, Krane N, Mitchell R (2019):** Relationship between drug-induced sleep endoscopy findings, tonsil size, and polysomnographic outcomes of adenotonsillectomy in children. Otolaryngol Head Neck

Surg., 161 (3): 507-513. doi: 10.1177/0194599819860777.

3. **Socarras M, Landau B, Durr M (2019):** Diagnostic techniques and surgical outcomes for persistent pediatric obstructive sleep apnea after adenotonsillectomy: A systematic review and meta-analysis. Int J Pediatr Otorhinolaryngol., 121: 179-187. doi: 10.1016/j.ijporl.2019.02.030.
4. **Singh P, Verma J, Singh J (2020):** Validation of Salivary Markers, IL-1β, IL-8 and Lgals3bp for Detection of Oral Squamous Cell Carcinoma in an Indian Population. Sci Rep., 10 (1): 7365. doi: 10.1038/s41598-020-64494-3.
5. **Mitri C, Xu Z, Bardin P (2020):** Novel anti-inflammatory approaches for cystic fibrosis lung disease: Identification of molecular targets and design of innovative therapies. Frontiers in Pharmacology, 11: 1-25. doi: 10.3389/fphar. 2020.01096.
6. **Filimon A, Preda I, Boloca A, Negroiu G (2021):** Interleukin-8 in Melanoma Pathogenesis, Prognosis and Therapy-An Integrated View into Other Neoplasms and Chemokine Networks. Cells, 11 (1): 1-28. doi: 10.3390/cells 11010120.
7. **Najdaghi S, Razi S, Rezaei N (2020):** An overview of the role of interleukin-8 in colorectal cancer. Cytokine, 135:1-10.Article 155205. doi: 10.1016/j.cyto.2020.155205.
8. **Sánchez M, Coveñas R (2022):** The Neurotensinergic system: A target for cancer treatment. Curr Med Chem., 29(18):3231-3260. doi: 10.2174/0929867328666211027124328.
9. **Singh M, Thakur M, Mishra M (2021):** Gene regulation of intracellular adhesion molecule-1 (ICAM-1): A molecule with multiple functions. Immunology letters, 240: 123-136. doi: 10.1016/j.imlet.2021.10.007.
10. **Russo R, Garcia C, Teixeira M, Amaral F (2014):** The CXCL8/IL-8 chemokine family and its receptors in inflammatory diseases. Expert Rev Clin Immunol., 10 (5): 593-619. doi: 10.1586/1744666X.2014.894886.
11. **Bhatt S, Guleria R, Kabra S (2021):** Metabolic alterations and systemic inflammation in overweight/obese children with obstructive sleep apnea. PLoS One, 16 (6): e0252353. doi: 10.1371/journal.pone.0252353.
12. **Metinko A, Kunkel S, Standiford T, Strieter R (1992):** Anoxia-hyperoxia induces monocyte-derived interleukin-8. J Clin Invest., 90 (3): 791-8. doi: 10.1172/JCI115953.
13. **Gozal D, Kheirandish-Gozal L(2008):** Cardiovascular morbidity in obstructive sleep apnea: oxidative stress, inflammation, and much more. Am J Respir Crit Care Med., 177 (4): 369-75. doi: 10.1164/rccm.200608-1190PP.
14. **Ohga E, Tomita T, Wada H *et al.* (2003):** Effects of obstructive sleep apnea on circulating ICAM-1, IL-8, and MCP-1. J Appl Physiol., 94 (1): 179-84. doi: 10.1152/japplphysiol.00177.2002.
15. **Andersson J, Abrams J, Björk L *et al.* (1994):** Concomitant in vivo production of 19 different cytokines in human tonsils. Immunology, 83 (1): 16-24. PMID: 7821961.
16. **Tam C, Wong M, McBain R et al. (2006):** Inflammatory measures in children with obstructive sleep apnoea. Journal of paediatrics and child health, 42 (5): 277-282. doi: 10.1111/j.1440-1754.2006.00854.x.
17. **Ke D, Kitamura Y, Lejtenyi D *et al.* (2019):** Enhanced interleukin-8 production in mononuclear cells in severe pediatric obstructive sleep apnea. Allergy Asthma Clin Immunol., 15: 23. doi: 10.1186/s13223-019-0338-1.
18. **Stewart M, Glaze D, Friedman E *et al.* (2005):** Quality of life and sleep study findings after adenotonsillectomy in children with obstructive sleep apnea. Archives of Otolaryngology–Head Neck Surg., 131 (4): 308-314. doi: 10.1001/archotol.131.4.308.
19. **Mitchell R (2007):** Adenotonsillectomy for obstructive sleep apnea in children: outcome evaluated by pre- and postoperative polysomnography. Laryngoscope, 117 (10): 1844-54. doi: 10.1097/MLG.0b013e318123ee56.