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Correlation between IL-8, IL-6 in tonsillitis patients and progressive of disease

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Abstract

Tonsil is the organ of the first line of host defense against pathogenic agents, but also a place with recurrent chronic inflammatory processes. It represents the effectors of systemic humoral and cellular immunity .So this study aimed to evaluate IL-8, IL_6 serum level in different types of tonsillitis and their correlation with development of disease. This study included 100 patients attending to Al-Sadder Medical city in ENT unit in Najaf governorate .The patients were classified into two groups: seventy patients with tonsillitis who were subdivided into acute tonsillitis, chronic tonsillitis and recurrent tonsillitis as well as thirty patients with tonsillectomy. Five ml of a venous blood sample was collected from each patient and control 2ml of blood put in EDTA tube for total and differential blood count and 3ml for ELISA testing to determine the level of IL-8 and IL-6.

This study has shown that higher frequency of tonsillitis in males (52.9%). The highest percentage of patients appeared with Grade 3 (33.6%), followed by Grade 2 (22.7%) in tonsillitis patients and grade 4(43.4%), grade 3(33.3%) in tonsillectomy patients. The level of IL-8, IL-6 was higher in tonsillitis patients and tonsillectomy than in healthy subjects. IL-8, IL-6 serum level was highly increased among the patients in grade 3, 4 (46.57, 50.65 pg/ml for IL-8 and 45.65 ± 5.61, 70 ± 4.32 pg/ml for IL-6) and highly significant increase in chronic and recurrent patients (28.87, 26.94 for IL-8) and (31.74, 29.54 for IL-6).

In conclusion there is a strong correlation between IL-6 and IL-8, furthermore, IL-8 strongly correlate with Monocyte count. IL-6 and IL-8 found to be increase along with tonsillitis severity i.e. the grade 3, 4 tonsillitis have high level of IL-6 and IL-8.

Key words: *Tonsillitis, Tonsillectomy, IL-6, IL-8, correlation*

I. Introduction

Tonsillitis is inflammation of the of tonsils characterized by redness, swelling of the tonsils lead to effect in physiological and immunological status of the patients. The most common type of tonsillitis; acute tonsillitis, chronic tonsillitis and recurrent tonsillitis (Najim *et al*., 2019). It may be associated with some complications such as

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peritonsillar abscess, acute otitis media, chronically infected tonsils interfere with children's sleep and streptococcal infection can cause rheumatic fever, glomerulonephritis and scarlet fever (Aziz *et al*. 2019). In Iraq it has been recorded that about 33% of tonsillitis cases were noticed in the age group 1-10 years, while the minimum rate (4.7%) was between 51-60 years (Nabat *et al.,* 2019).

Brodsky grading scale, classified palatine tonsils preoperatively into 5 grades as follows: grade 0 indicated the previous tonsillectomy; grade 1 indicated that the tonsils were hidden in the pillars; grade 2 indicated that the tonsils were beyond the anterior pillar and between 25 and 50% of the pharyngeal space; grade 3 indicated that the tonsils were beyond the pillars but not to the middle and occupied >50% and up to 75% of the pharyngeal space; grade 4 indicated that the tonsils occupied >75% of the pharyngeal space (Lu *et al*., 2018).

Interleukin 6 (IL-6) is a pleiotropic cytokine of 184 amino acid that exerts multiple functions in the body, IL-6 synthesis and secretion is induced during inflammatory conditions such as upon stimulation of toll like receptor (TLR) 4 by lipopolysaccharide or upon stimulation of cells by IL-1 or TNF-α (Schmidt-Arras and Rose-John, 2016). Interleukin-8 (IL-8 or CXCL8) is a pro-inflammatory CXC chemokine produced by various cell types to recruit leukocytes to sites of infection or tissue injury. In cases of acute and chronically infected tonsils, accumulation of certain subsets of chemokines and neutrophilic dynamics has been observed (Brandtzaeg, 2010). The study aim to evaluate IL-8, IL-6, blood parameter in tonsillitis patients and their correlation with progressive the disease.

II. Materials and Method

Study subjects and sample collection

A total 100 patients and 30 apparently healthy subjects were included in this study; Patients admitted to Al-Sadder Medical City, ENT unit, in Al–Najaf province during the period from August to December 2019. The Patients were classified into two groups: seventy patients with tonsillitis who were subdivided into (36) as acute tonsillitis, (23) patients with chronic tonsillitis and (11) with recurrent tonsillitis as well as thirty patients with tonsillectomy.

Five ml of a venous blood sample have been collected from each patient and control groups, and split into two tubes, the first one; 2 ml whole blood was dispensed with EDTA tubes to investigate complete blood count (CBC) using hem analyzer system (Semex, japan). The second portion (3ml) was transferred into gel tube, left 10 minutes then centrifuge at (3000 rpm) for 10 min, and the serum was collected in sterile Eppendorf tubes in tow repeaters and kept frozen at -20 C˚for ELISA testing to determine the level of IL-6, IL-8 according to (Elabscience, USA).

Ethical approval: This study was ethically approved by the medical ethics committee in Al-Sadder medical city, Najaf, Iraq (approval NO.:7539). Moreover, adult patients and the parent of the children patients gave the informed consent before they gave the samples.

Statistics analysis: The results are presented as means and statistical with standard error (S.E.) and were analyzed using one-way analysis of variance (ANOVA) test via Graphpad prism 5.04. $p < 0.05$ was considered significant.

III. Results

Distribution of study subjects according to type of disease and gender

A total of 100 patients with tonsils infection that divided into two main group, 70 (70%) tonsillitis patient that further divided into acute tonsillitis with 36 (51.4%,), chronic tonsillitis were 23 (32.8%) and recurrent tonsillitis were 11 (15.8%) and 30 (30%) tonsillectomy patients, In addition to 30 apparently healthy subjects as controls group as show in table (1). The gender distribution revealed that male more frequent than female as show in table (1).

Table (1): Distribution the study subjects according to type of disease and gender

Sex	Tonsillitis			Tonsillectomy No (%)	Control
	Acute No (%)	Chronic No (%)	Recurrent No (%)		
Female	16(44.4%)	11(47.8%)	6 (54.5%)	14 (46.7%)	15
Male	20(55.6%)	12 (52.2%)	5 (55.5%)	16 (53.3%)	15
Total	36	23	11	30	30

Distribution of patients according to grade of disease

Patients with Tonsillitis are divided into several grades with different numbers and percentages, the highest percentage of patients appeared with Grade 3 (42.8%), followed by Grade 2 (31.4%), Grade 1 (20%), and Grade 4 (5.8%), While in tonsillectomy the grade 4 (43.4%) and 3 (33.3) was high frequency then Grade 2(23.3%) as shown in figure (1).

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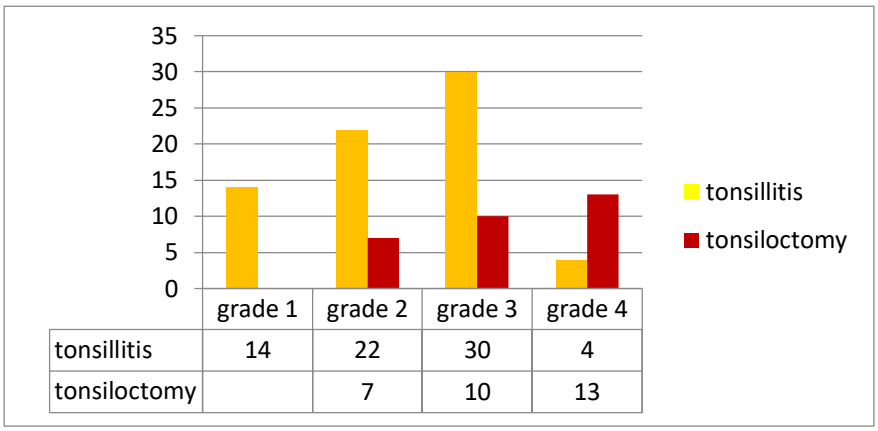

Figure (1): distribution of patients according to grade of disease

Estimation the level of IL-8 and IL-6 in patients and controls

The result indicated that a significant difference in the serum level of IL-6 between patients and healthy controls. It is clear that IL-8 and IL-6 has been increased in the serum of Tonsillitis patients to 74.28, 86.31 pg/ml, tonsillectomy patients 82.05, 93.65 pg/ml in compared with 18.77, 23.94 pg/ml in healthy control as shown in figure (2).

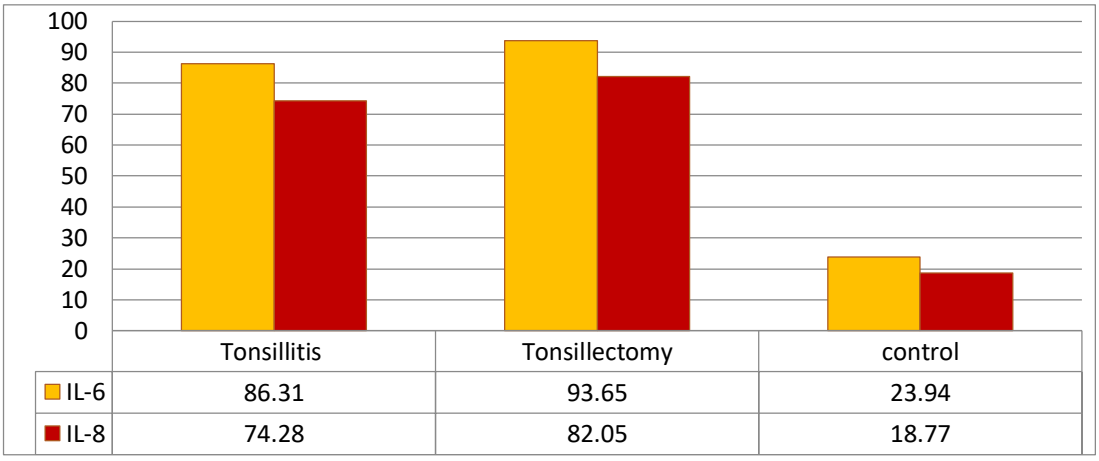

Figure (2): the levels of serum IL-8 and IL-6 levels in tonsillitis, tonsillectomy patients and healthy controls.

The result indicated increased serum level of IL-8, IL-6 in acute tonsillitis patients was (20.64, 25.34) and highly increased in chronic, and recurrent tonsillitis patients, which about (28.87, 31.74) pg/ml, (26.94 29.54 ± 3.78) pg/ml respectively as shown in figure (3).

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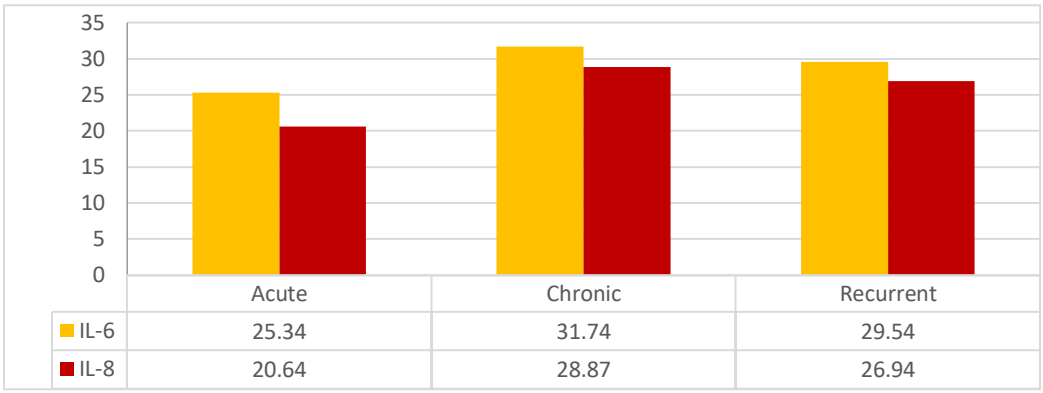

Figure (3): IL-8 and IL-6 levels in acute, chronic and recurrent tonsillitis patients

Evaluation IL-8 and IL-6 level in patients according to grade of disease

The present study show there is statistically significant increase ($P \leq 0.05$) in IL-8, IL-6 serum level in patients with advance grade in compare with less grade as show in figure (4)

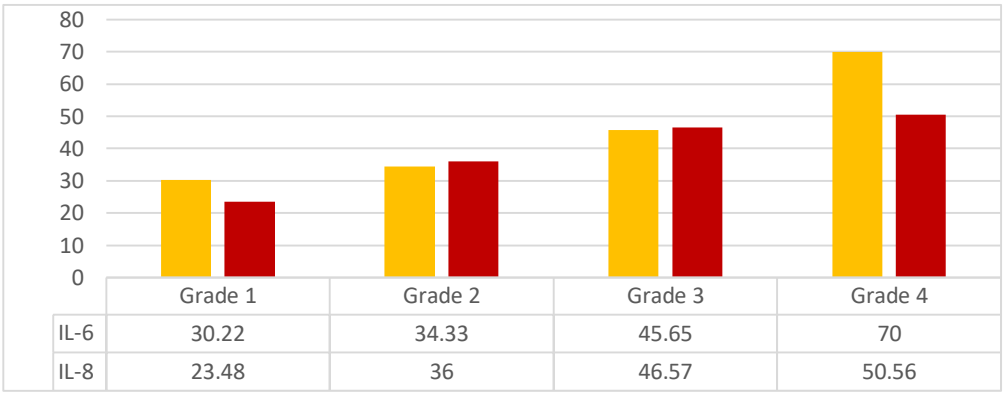

Figure (4): The percentage of serum level of IL-8, IL-6 in patients according to grades of disease

Blood parameter

The results show significantly increased in the number of white blood cells, number of neutrophils and lymphocyte in tonsillitis patients compared to control, and the number of neutrophil increased significantly in the tonsillitis patients compared to tonsillectomy and control group ($p > 0.05$) as shown in table (2).

Table (2): Mean level of blood parameters in tonsillitis patients compared with control group

Mean ± S.E.			
Blood parameter	Healthy subjects	Tonsillitis patients	Tonsillectomy Patients
WBC count	8455 ± 32.44	11.640 ± 45.27	10.420 ± 58.78

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Neutrophil count	4618 ± 27.59	8050 ± 47.90	6240 ± 44.12
Monocyte count	168 ± 31.89	348 ± 19.66	416 ± 17.44
Lymphocyte count	1680 ± 26.33	2900 ± 25.95	3640 ± 32.86

The results appear a significant increase ($P < 0.05$) in total WBC count in acute tonsillitis patients (13.100 ± 45.55) then in chronic (11.900 ± 67.60) and recurrent patients (10.500 ± 89.44). Also results of differential blood count appear that Neutrophil count were highly increased in acute patient (9.000± 56.3) while, Lymphocytes count highly increased in recurrent patients (3195 ± 85.94) as show in table (3).

Table (3): Mean level of Blood parameters in acute, chronic and recurrent tonsillitis patients compared with control group

Mean ± S.E.			
Blood parameter	Acute T.	Chronic T.	Recurrent T.
WBC count	13.100 ± 45.55	11.900 ± 67.60	10.500 ± 89.44
Neutrophil count	9.000± 56.3	8678 ± 62.78	6472 ± 48.93
Monocyte count	400 ± 29.77	331 ± 27.33	316 ± 37.45
Lymphocyte count	2620 ± 89.13	3000 ± 76.56	3195 ± 85.94

Correlation among the immunological parameters

Table (4) illustrate the correlation coefficient among the immunological parameters. The results of this study showed that the interleukin 8 has a positive correlation with neutrophil count (r= 0.332) (Figure 5), and lymphocyte count (r= 0.345) (Figure 6). While it is strongly correlated with monocyte count (r= 0.475) (Figure 7). IL-6 was strongly correlated with IL-8 (r= 0.978) (Figure 8).

Table (4): Correlation coefficient among the immunological parameters

Correlation	r-value	p-value
IL-8 and Neutrophil count	0.332*	0.048

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IL-8 and Monocyte count	0.475**	0.003
IL-8 and Lymphocyte count	0.345*	0.039
IL-6 and IL-8	0.978**	0.0001

* Significant correlation at the level of significancy (0.05)

** Significant correlation at the level of significancy (0.01)

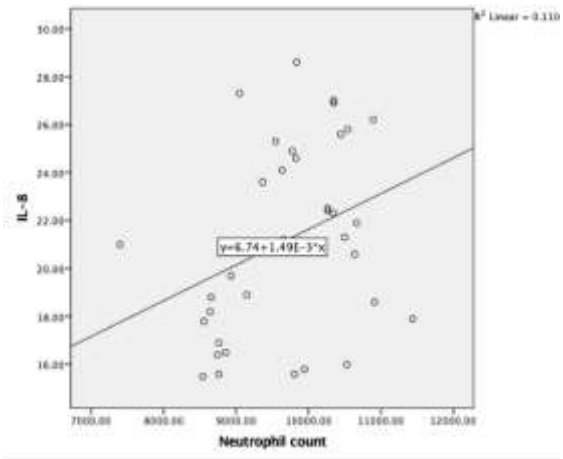

Figure (5): correlation between IL-8 and neutrophil count

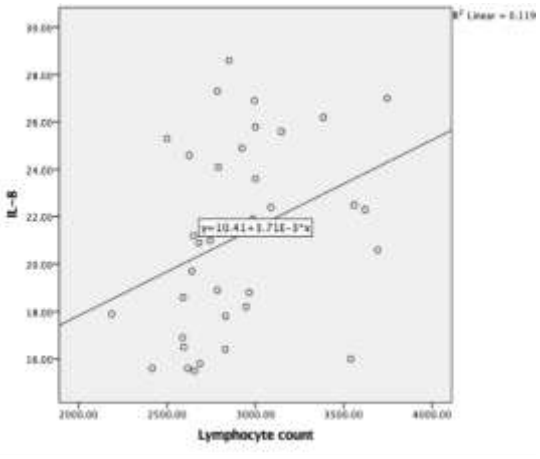

Figure (6): correlation between IL-8 and lymphocyte

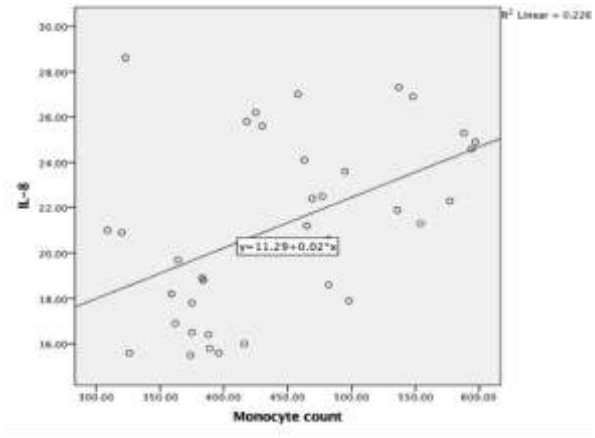

Figure (7): correlation between IL-8 and monocyte

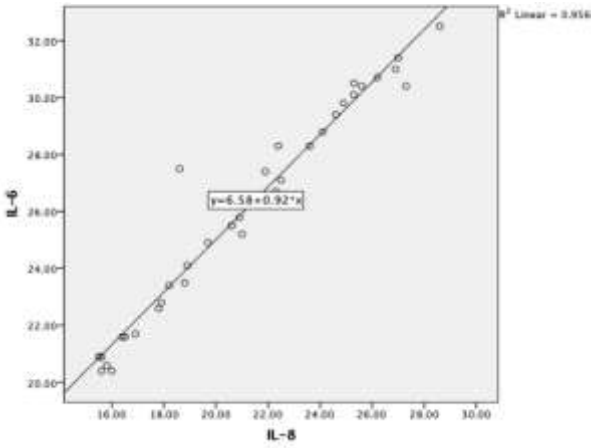

Figure (8): correlation between IL-6 and IL-8

IV. Discussion

Tonsillitis has significant impact on health status and quality of life as it causes significant morbidity and time lost for school or work.

Distribution of study subjects according to type of disease and gender

This study showed high incidence in acute tonsillitis than other type of tonsillitis and in men than female. Bista *et al*. (2006) showed the distribution of tonsillitis was more in male patients (55%) compared to female patients (45%). In addition, the present study in line with Cavalcantia *et al*. (2019) who confirmed that male recorded 53.7% of tonsillitis patients and 46.3% female. Sankri-Tarbichi, (2012) explained that the male gender as risk factor for OSA**.**

Distribution of patients according to grade of disease

The grade of the palatine tonsils is usually defined by the volume of space that is claimed by the tonsils in the pharyngeal airway and several most patients present with either an excess amount of soft tissue or an under developed bony skeleton that leads to the narrowing of the pharynx (Ryan and Bradley, 2005). This results is similar to Lu *et al*. (2018) who founded that males have been more than females patients and the grade 2 and 3 the highest incidence then grade 1 and 4 with frequency 35.3%, 34.1%, 28.2%, and 2.4% respectively and illustrated that patients with greater tonsil grade were likely to benefit from tonsillectomy with additional changes in the pharyngeal cavity. Therefore, tonsil grade obtained via physical examination was conducive to select surgical candidates with a high success rate of treatment (Lu *et al*., 2018). Jara and Weaver, (2018) reported a strong correlation between tonsil grade and tonsil volume in adult and children patients with sleep disorders, breathing, and chronic tonsillitis. Brodsky, (1989) found majority of the patients who sought surgical intervention had grade 3 tonsillar hypertrophy (66%). Tonsillectomy to be effective in reducing the occurrence of throat infection (Paradise *et al*., 2002). Ng *et al*. (2010) confirmed that patients with tonsil grades 3 and 4 had a significantly greater volume than those with grades 1 and 2, which revealed that patients with greater tonsil grade were likely to choice tonsillectomy.

Estimation the level of IL-8 and IL-6 in patients and controls

Skovgaard *et al*. (2009) observed IL-6 were significantly induced after infection in most tissues of tonsils. The high concentrations of IL-1, IL-6 and TNF-α in adenotonsillar tissues, believing it to be an expression of local overproduction due to monocyte-macrophage activation resulting from repeated stimuli from pathogen agents (Passàli *et al*., 2003). Skovbjerg *et al*. (2015) showed tonsillar secretions from patients with acute tonsillitis had significantly higher levels of IL-1β, IL-6, IL-8, IFN-γ, and PGE2. IL-6 and IL-1β were the most strongly elevated cytokines in tonsillitis patients. In 2018, Zhou *et al.* found significant increase of TNF-α and IL-6 serum levels in the acute pharytonsilitis, compared with control group. In addition, Ünal *et al.* (2002) evaluate serum interleukins IL-1β, IL-4, IL-6, and IL-8 in chronic tonsillitis patients before and after tonsillectomy and found that IL-1β and IL-6 levels were significantly higher than the control levels ($p < 0.05$) in preoperative serum samples.

This study confirmed by (Sachse *et al*., 2005) they found that level of IL-1β, IL-6, and IL-8 were higher in serum of recurrent tonsillitis as well as IL-8 in peritonsillar abscesses. Seethaler *et al.*, (2020) explain that higher levels of IL-8 and IFN-γ in serum level in both tonsillectomy and tonsillotomy patients in compare with healthy subjects.

Windfuhr *et al.* (2016) revealed that an associated between outcome of tonsillectomy and level of IL-8 so high serum level associated with less improvement in QoL after TE/TO. Macdonald *et al*. (2014) observed an elevation of IL-8 in acute infections and therefore anticipated for tonsillar disease. In 2018, Mandapathil *et al*. observed IL-8 expression was significantly elevated in acute infected tissue and chronic tonsillitis compared to hyperplastic tonsils ($p < 0.05$).

Evaluation IL-8 and IL-6 level in patients according to grade of disease

This study confirmed that mean serum level of IL-6 were higher in grade 3, 4. This result is similar to study done by (Yuko, 2012) who found that grade 4 was high frequency than other in tonsillectomy patients as well as the serum level of IL-6 was higher than other grade. Also, IL-6 levels to be higher in severe as compared to mild infection (Gentile *et al*., 2003). The higher IL-6 levels with grade 3 and 4 tonsils may be due to increased tissue bulk as hyperplastic tissue that activate most of immunologic function (Mehra and Redline, 2008).

High levels of IL-8 in serum of tonsillectomy patients may indicate progress of disease such as hypertrophy or respiratory syncytial virus infection and advance grades (3,4) which continue to have a negative impact on the patient's with QoL after TE/TO (Russell *et al*., 2017). Bird *et al.* (2014) explain that IL-8 highly increased in advance score and this illustrated the progress of disease.

Blood parameter

In this study, the results appear a significant increase ($P < 0.05$) in total WBC count in acute tonsillitis patients then in chronic and recurrent patients. Neutrophils represent a multifunctional cell type that play main role in the innate immune response against extracellular pathogens and their toxin products by recognition, phagocytosis and killing. On the other hand, long-lived mononuclear cells Monocytes and Macrophages, are front line soldiers to eradicate obligate intracellular pathogens. However, the overall production of PMNLs in circulating cells is markedly increased during infection and inflammation (Rosales *et al*., 2016).

A study in 2017 from Turkey by Elmas *et al*. involving 150 children found significantly higher WBC, Neut., and CRP in group A Streptococcus -positive tonsillitis patients. A study from Denmark in 2014 by Christensen *et al*. investigated 100 patients 15–40 years of age who had acute tonsillitis and found significantly elevated mean values of CRP, WBC, and absolute neutrophil count compared with healthy group.

The results indicated an increase in the total number of white blood cells in people with acute and chronic tonsillitis compared with the control group and this observed is an agreement with (Christensen *et al*. 2014). Also agree with Abd ALaziz *et al*. (2019) they confirmed that complete white blood count and differential count showed statistically significant changes in the presence of tonsillitis and founded that number of neutrophils were highly increase in acute patient while number of lymphocyte increase in recurrent tonsillitis patients compared to control.

The infection of the tonsils lymphatic tissue with bacteria lead to migration of monocyte from the blood stream to inflamed site and it may lead to increase in the number of monocyte (Abbas *et al*., 2018. CRP, WBC and total neutrophil counts were significantly higher in patients who had scores ≥3 and positive GAS throat cultures than in patients negative for GAS ($p < 0.05$) (Akin- Ocal *et al*., 2017).

Neutrophils are essential for cytokine production in acute process in inflammatory disorders while lymphocyte is important for cytokine production in chronic process in inflammatory disorders (Wang and Arase, 2014).

Correlation among the immunological parameters

Weitkamp *et al*. (2002) confirmed a significant correlation between concentrations of IL-6 and IL-8 in serum which consider as diagnostic markers for neonatal bacterial infection. Also, Alwakil *et al*. in 2011 concluded a relationship between IL-6 and IL-8 serum level and both involved in the pathogenesis of asthma when increased their production. Interleukin-8 (IL-8) also referred to as neutrophil activating protein I (NAP-I) has major actions as a neutrophil chemo-attractant and activator. Gong *et al*. (2020) they observed a significant associated between disease severity and increased level of IL-6, IL-8 or both in Pneumonia patients. Naskalski *et al*. (2007) they mention an interrelation between monocytes and IL-8 in days 2 and 3 of bacterial infection of acute pancreatitis patients and confirmed that a relationship between direct count of peripheral blood leucocyte populations and plasma concentrations of IL-6, IL-8. Park *et al*. (2000) they explain that Lymphocyte numbers and IL-6 levels in Broncho alveolar Lavage Fluids were higher in pneumonia patients.

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