

# Serum Level of Several Cytokine in A Sample of Iraqi Patients with Prostate Disease

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## Abstract

The gland that the male bladder necks cover is the prostate. It preserves some seminal fluid and aids males in ejaculating during sexual activity. Three conditions that typically affect them are inflammation, benign enlargement, and prostate cancer. In order to investigate the relationship between cytokine levels (IL6, IL8, IL37 and TGF  $\beta$ ) and the severity of prostate diseases by Sandwich ELISA is the most commonly used format because it is highly specific, flexible, sensitive and suitable for complex samples, 180 people were divided into four groups for 45 each one, The results of the study showed a strong correlation between high cytokine levels and disease severity, suggesting that it is possible to use this relationship as a gauge for how the prostate disease is progressing.

**Keywords:** BPH, PCA, Prostatitis, IL8, IL6, IL37 and TGF  $\beta$

## 1. Introduction

Most cases of prostate disease are found in elderly persons, as a result of cellular proliferation in the region of the prostatic tissue surrounding the urethra (Cai et al.,2019; Cannarella et al.,2021). Prostate cancer is the second most frequently diagnosed cancer in males worldwide and the second major cause of cancer death in men. In 2019, 174,650 new PCa cases were discovered statewide, and the disease caused 31,620 lives in men (El Ezzi et al.,2020; Miyake et al.,2022). Prostatic inflammation due to the local microenvironment, which is filled with cytokines and growth factors connected with numerous types of neoplasia (Bardan et al.,2014). Third type of prostate disease is benign prostatic hyperplasia (BPH) which typically affects men, rises with advancing age, the non-malignant enlargement of the prostate gland, which most commonly affects men over 40, is what distinguishes it according to estimates, BPH affects 20 % of men in their 40years, up to 60 % of men in their 60 years and 70 to 80 years causes 90 % of men (Taha et al., 2020). cytokines is a large family of proteins, characterized by low molecular weight, represent the chemical messengers for cell-to-cell communication, that are produced as membrane-bound or released proteins (Najem et al.,2020). Patients' serum and prostate discharge fluid contain soluble cytokines that control the innate and adaptive immune response. Different cytokines are implicated in the microenvironment of immune cells and tumors, which may have an impact on tumor progression (AlChalabi et al.,2020). When cytokines bind a number of downstream proteins are activated in response to receptors on target cells, changing target cell gene expression patterns and inducing desirable responses (Altan-Bonnet et al.,2019). According to numerous studies that have identified IL-6 as a prognostic factor in prostate

cancer (Adekoya et al.,2020). IL-37 It is commonly known that inflammation and carcinogenesis go hand in hand, Numerous studies have revealed that IL37 an anti-inflammatory cytokine (DeStefano et al.,2015).IL8 is another cytokine elevated with prostate disease specially in the malignant, initiates its activity by binding with the G protein-coupled receptors CXCR1 and CXCR2, that are primarily found on cancer cells( Roller et al.,2020).The clinic-pathological aspects of TGF-B expression for prostate cancer may be useful Our prior research suggests that TGF-B expression in the prostate may serve as prognostic indicators for prostate cancer(Torrealba et al.,2019).

## 2. Experimental Methods (Sample, Patients & Healthy Individuals)

The study's sample of 180 men examined the urology section at Al-Yarmouk Teaching Hospital in Baghdad between October 1, 2021, and January 1, 2022. Depending on their diagnostic techniques, the subjects were divided into four categories, control, prostatites, benign and malignant every group was 45.

### 2.1 Experimental design

The auto analyzer and ELISA reader were used to estimate serum levels of diagnostic immunological parameters. The serum was separated and divided into Eppendorf tubes until the estimation for cytokines by the Elisa technique, It was then centrifuged for five minutes at 3000 rpm. At -20°C, the serum was stored until it was needed. In the current investigation, the cytokines levels discovered in the blood of prostate disease patients and controls were evaluated making use of the enzyme-linked immunoassay assay (ELISA), which employed in conjunction with an ELISA kit made by Chinese businesses.

## 2.2 Statistical Analysis

SPSS (version for Windows, version 26 was used for all calculations (SPSS Inc. Chicago, Illinois, United States). To express continuous variables, the mean and standard deviation were utilized (SD). Group discrepancies were examined using the student's t-test. A p-value of 0.05 or less was used to determine whether statistics were significant.

## 3. 3. Results and Discussion

In clinical settings, cytokines are used as noninvasive diagnostic markers for disease prognosis, for the pathophysiology of numerous inflammatory diseases, and to track the effectiveness of treatments

(Chung et al.,2019). Prostate diseases are the most common age-related disease in men and are characterized by chronic inflammation that is strongly linked to both benign and malignant conditions of the prostate. This accumulation of immunocompromised individuals' cells that secrete different cytokines means creating the ideal conditions for the progression of various diseases, particularly cancer. In this investigation, the serum levels of numerous cytokines (IL-37, IL-8, IL-6 and TGF- $\beta$ ) were estimated ( AlChalabi et al.,2020).The mean value  $\pm$  SE IL8, IL6, IL37and TGF  $\beta$  for control, benign, malignant and Prostatic prostate tumor respectively are shown in table (3-1).

**Table (3-1): Levels of IL8, IL6, IL37and TGF  $\beta$  in patients group and healthy volunteers.**

Groups	Mean of TGF- $\beta$ $\pm$ SE (pg/ml)	Mean IL-37 $\pm$ SE (pg/ml)	Mean IL-6 $\pm$ SE (pg/ml)	Mean IL-8 $\pm$ SE (pg/ml)
PCa	107.33 $\pm$ 4.98A	15.61 $\pm$ 0.34A	22.59 $\pm$ 2.04A	156.43 $\pm$ 18.52A
BPH	85.98 $\pm$ 1.22B	12.52 $\pm$ 0.35B	18.54 $\pm$ 0.65B	117.87 $\pm$ 6.38B
Prostatitis	46.11 $\pm$ 3.36C	16.07 $\pm$ 1.12A	13.32 $\pm$ 1.38C	88.16 $\pm$ 1.17C
Control	38.06 $\pm$ 0.75C	11.43 $\pm$ 0.70B	4.76 $\pm$ 0.34D	35.95 $\pm$ 0.70D

\*Different letters in columns represents significant difference ( $p < 0.001$ ).  
\* Non-significant difference ( $p > 0.05$ ) is shown by similar letters in columns.

IL-8 is functional and expressed in situ by epithelial and stromal prostate cells, indicating to its involvement in disease pathogenesis, and is the most exact and prognostic surrogate marker for identifying prostate inflammatory disorders, such as CP/CPPS and BPH. BPH prostate tissue is recruited cells with the proper receptors. (Penna et al.,2007). In expressed prostatic secretions (EPS) from chronic prostatitis, higher amounts of IL-8 were detected (CP) (Dung et al.,2018). Another study showed relationship with the immunoreactive IL-8 concentrations in patients with BPH or PCa (Woo et al.,2014). Maynard et al.,(2020)observed Men with prostate cancer have higher serum levels of IL8, which is linked to worse outcomes, According to another research, stroma surrounding prostate cancers has higher levels of IL8 protein expression than stroma surrounding prostate epithelium that seems to be normal we do not have a complete description of the difference in IL8 production and expression in tumor-versus-benign regions in terms of cell location ,study showed elevated serum IL8 expression in three groups and significant different with control this agreement with research as mentioned above.

In prostate tumors, IL-6 and its particular receptor (IL-6R) control a variety of biological responses. This is most likely due to IL-6's ability to promote pro- and anti-inflammatory responses and interact with a variety of target cells to generate autocrine and paracrine effects in prostate tissue. Several recent studies back up the idea that IL-6 plays a crucial role in the pathophysiology of prostate tumors (Ene et al.,2022). Among the cytokines, IL-6 might be essential to the pathological approach of prostatitis, there were studies revealed that in patients with prostatitis, the levels of IL-6 was significantly related to their symptoms (Milicevic et al.,2015). The another

study found that IL-6 and IL-8 levels were obviously greater in prostatitis patients, which was consistent with the findings of other investigations (Cai et al.,2017,Engelhardt et al.,2015).Fibbi et al.,(2010) As according studies, BPH-related inflammatory processes might cause prostate stromal cells to release IL-6, which promotes the proliferation of prostatic tissues, agreement with our study showed elevated serum level IL6 in three groups and significant different with control.

Another cytokine increases immune cell differentiation and proliferation while inhibiting the antitumor immune response. TGF- $\beta$  expression is increased in cancer cells (Meng et al.,2018). interleukin expression in combination with prostate inflammation may cause sensitization of afferent neurons innervating the prostate, increasing sensitivity to pain and unpleasant sensations in the prostate and bladder as well as heightened sensitivity to bladder filling (Altan-Bonnet et al.,2019). The prostate tumor is also angiogenesis-promoting when TGF- $\beta$  is overexpressed in tumors (Chen et al.,2020). The mean serum level of TGF $\beta$  in three groups was significantly higher as compared with healthy control with mean level (38.10a $\pm$ 4.81vs G1 86.10b  $\pm$ 8.07, G2 105.21c $\pm$ 32.79, G3 48.99d $\pm$ 24) pg/ml, respectively.

More recently, Ding et al., (2017) demonstrate that there is no obvious change of prostate cancer cell proliferation or apoptosis in the presence of exogenous IL-37 in vitro . IL-37 is anti- or pro-carcinogenic such a discrepancy encourages speculation that IL-37 may have two effects on how prostate cancer develops., which may be related to stage and/or other risk factors or may promote cancer growth. It appears likely that this also increases the radio sensitivity of the cancer cells and radiation therapy may have a beneficial therapeutic

effect (Bao *et al.*, 2022). According to one study, IL-37 could boost prostate cancer cells' radio sensitivity by down-regulating the expression of cyclin-dependent kinase and up-regulating the expression of protein p27, Fas, and bax. This was found to be true even though IL-37 had few direct impacts on the viability of prostate cancer cells (cdk2), the findings conducted by Zhou *et al.*, (2019). IL37 has been proposed as a possible radio sensitizing agent for the treatment of prostate cancer. While higher levels of IL37 were found in three groups in our investigation and a significant difference with the control group was observed, there was no difference between the prostatitis and malignant groups with the control group and the benign groups.

#### 4. Conclusion

Based on the findings of this study, serum cytokines concentration and prostate disease in different types may be better diagnostic tools for this disease than other traditional risk factors. They may also be added to routine examinations of prostate disease patients to serve as a foundation for customized treatment.

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