EVALUATION SOME OF IMMUNOLOGICAL PARAMETERS IN BENIGN PROSTATIC HYPERPLASIA PATIENTS TREATED WITH 5 ALPH-REDUCTASE INHIBITOR (FINASTERIDE)

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ABSTRACT

In order to evaluate the levels of PSA, IL-17 ,and CRP in BPH patients, (60) BPH patients, and (30) healthy man as control group were involved in the current study ,their ages (the control and patients) were between (40-59) years old. All of them living in Amara city .Estimation of PSA,IL-17 and CRP in serum were achieves before and after 3 month of treatment by 5 -α reductase (finasteride) ,and the results shown that there were a significant decreased (P<0.01)in serum PSA in post-treatment group compared to pre-treatment , which was higher than control group .in addition ,IL-17 level was increased significantly (P<0.05)in comparison with post-treatment and control group , also the CRP level (positive) was increased in pre-treatment group compared to post-treatment and control group .In conclusion the BPH effect on level serum of PSA,IL-17 and CRP by significant increased, while the finasteride causes significant dcreased in theri levels after 3 month of treatment.

Keywords: BPH, PSA, IL-17, CRP

INTRODUCTION

BPH represents the most common nonmalignant condition of the abnormal growth of prostatic cells in aging men (Sahi, *et al*., 2013; Husain,*et al*., 2016). It is considered as a common public health problem, causing high morbidity and essential worsening of men's quality of life. (Lu andChen, 2014), and could be qualified clinically or pathologically.

The association of benign prostatic hyperproliferation with immune dysregulation and chronic inflammation has offered an alternative framework in which investigators hope to understand BPH (Steiner *et al*., 2003).

The prostate specific antigen (PSA) is produced primarily by epithelial cells (Matthew *et al*, 1998; Adekola, 2013). The prostate gland manufactures these proteins in large quantities which are concentrated in the prostatic tissue and consequently serum (PSA) levels are normally very low (American Urological Association, 2000). Normally a little (PSA) leaks from the prostate into the blood (Brawer, 1995). If the prostate is enlarged then the leakage appears exaggerated. This is probably why the (PSA) can be increased in men with enlarged prostate who do not have cancer.

Prostatic inflammation observed in BPHmay cause cytokine release from inflammatory cells and condition of relative hypoxia resulting from the increasing oxygen demand of proliferating cells that may end up in tissue injury (Nunzio,*et al*.,2011),cytokines and growth factors released from inflammatory cells may not just interact with immune effectors but also with stromal and epithelial cells of the prostate (Robert,*et al*., 2009).

Regulatory derangement in BPH also occurs at another level via the pro-inflammatory cytokine IL-17.This cytokine, which is increase in activated T lymphocytes and perhaps in epithelial and smooth muscle cells in BPH (Lee and Peehl, 2004).

C-reactive protein (CRP) was the first acute phase protein tobe described and comprises the nonspecific physiological and biochemical responses to most forms of tissue damage, infection, inflammation, and malignant neoplasia (AL-Taee,2005).If inflammation in the prostate leads to prostatic growth, and if systemic CRP levels reflect prostatic inflammation, correlations between CRP levels and rapid changes in prostatic growth might be observed (Ghazi ,2012). This search aimed to evaluate PSA,IL-17 and CRP in BPH patients before and after finasteride treatment.

MATERIALS AND METHODS

This study was carried out at the AL-Sadder Teaching Hospital/Missan, in the period from April 2015 to April 2016,including (40) patient with mean age (53.25±4.85) who had Benign Prostatic Hyperplasia, this group considered as pre-treated group (1^{st} group) (before treated with finasteride drug 5mg/daily), and post-treated group (2^{nd} group)which treated with the finasteride drug 5mg/daily for 3 month .Beside these two groups, we have another (40)healthy man with mean age (48.9±5.1)which as control group (3^{rd} group) .

Experimental Design

Patients completed a previously validated baseline questionnaire. Prostate size and configuration was determined by DRE and ultrasounds (transabdominl). Patients were treated with a 5mg/day dose of finasteride for at least 3 month, the blood collection from the patients before start with drug (pretreated) and after 3 month of the treatment (post treated).

Collection of Blood Sample

5ml of venous blood were collected from the patients and control group at (8-10 AM), the blood sample was left for around 15 minutes to clot at room temperature, and then separated by centrifugation at (3000 rpm) for (5 min), collect serum to perform the following tests:

Measurement of Serum Total Protein Specific Antigen (TPSA)

Total PSA level was measured using VIDAS instrument and commercial kit based on ELFA technique (Enzyme Linked Fluorescent Assay).using kit manufactured by BioMerieux company (BioMerieux,2015) **.**

Measurment of Serum Cytokines IL-17

Serum level of cytokine (IL-17) was quantitatively estimated in serum of BPH patient and healthy control by ELISA method using ready kits manufactured by Elbascience company (Elbascience, 2014).

Measurement of Serum C - reactive protein (CRP)

The CRP-latex is a slide agglutination test was used for the qualitative and semi-quantitative detection of C-Reactive Protein in human serum. Latex particles coated with goat IgG anti-human CRP are agglutinated within 2 minutes when mixed with samples containing CRP. (Fisher and Nakamura, 1976).

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RESULTS

Total Prostate Specific Antigen (TPSA)

The results revealed that TPSA level in the 2nd group was (2.21± 1.40 ng/ml) decreased significant(P<0.05) comparison with 1st group (3.34± 2.62 ng/ml) and not significant compared to 3rd group (1.62±1.10ng/ml), the later decreased significantly(P<0.01) comparison with 1st group , table (1),figure (1).

Table 1. The effect of finasteride drug on the levels of serum PSA and IL-17 in study groups

parameters	*1st group*	*2nd group*	*3rd group*	*P value*
TPSA(ng/ml)	a 3.34 ± 2.62	b 2.21± 1.40	b 1.62 ± 1.10	0.004 **
IL-17 (pg/ml)	a 260.93 ± 102.47	b 27.5 ± 10.34	b 21.19 ± 7.25	0.000**

The values represent Mean ± SD
different letters refer to significant differences between groups
Similar letters refer to no significant differences between groups
**P<0.01 is significant

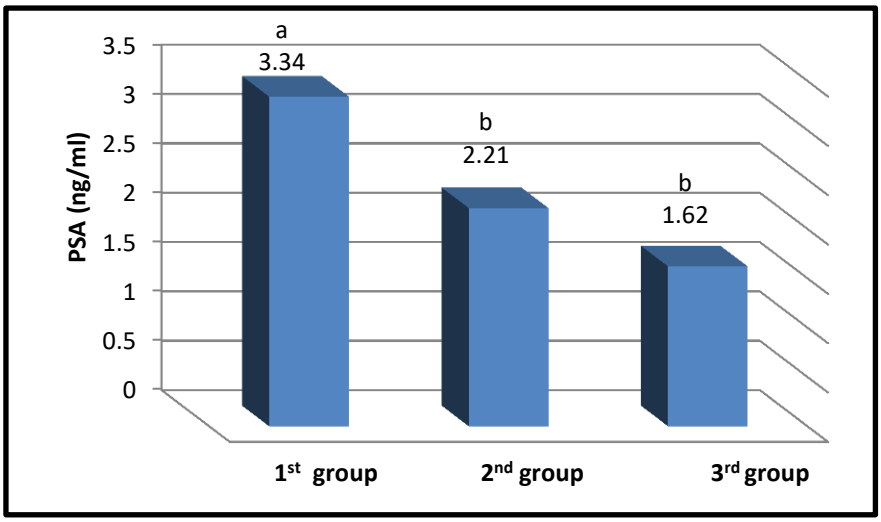

Figure 1: The effect of finasteride drug on the level of serum PSA for treated groups

Interleukin-17 (IL-17)

The results revealed that level of IL-17 in 1st group was (260.93±102.47 pg/ml) increased significantly(p<0.01) compared to 2nd group (27.5 ± 10.34 pg/ml) and 3rd group (21.19 ± 7.25 pg/ml) ,but no significant differences between 2nd and 3rd group , table (1) figure (2).

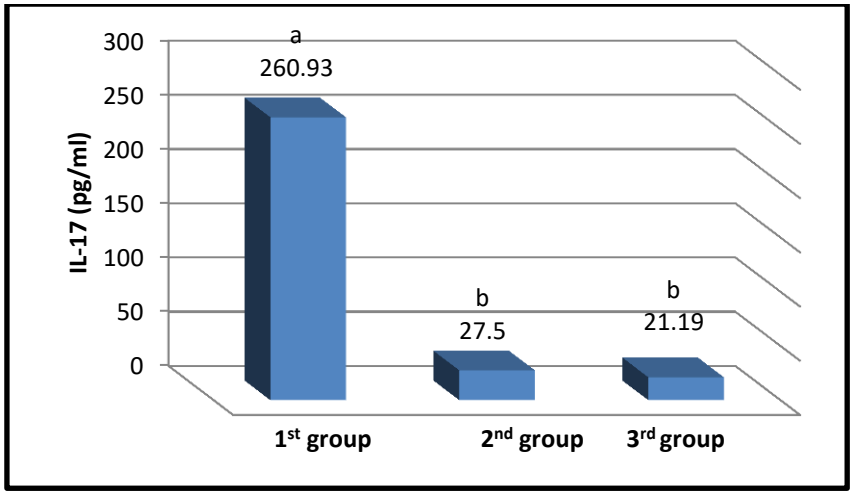

Figure 2: The effect of finasteridedrug on the level of serum IL-17 for the treated groups

C-RreactiveProtein (CRP)

Significant increased (P<0.05) positive percentage of CRP level in 1st group (16.67%) compared to 2nd group (6.67%) and 3rd group (10%).Also there was significant difference(P<0.05) in negative percentage between 1st group (83.33%) , 2nd group(93.33%), and 3rd group(90%), table (2) figure (3).

Table 2. The effect of finasteride drug on the percentage of positive CRP in treated groups

Parameters		*1st group*		*2nd group*		*3rd group*		*P-value*
		No.	%	No.	%	No.	%	
CRP (mg/L)	*Positive*	5	16.67	2	6.67	3	10.00	0.0473 *
	Negative	25	83.33	28	93.33	27	90.00	0.0473 *
Total		30	100%	30	100%	30	100%	---
P-value		0.0001 **		0.0001 **		0.0001 **		---

* (P<0.05), ** (P<0.01).

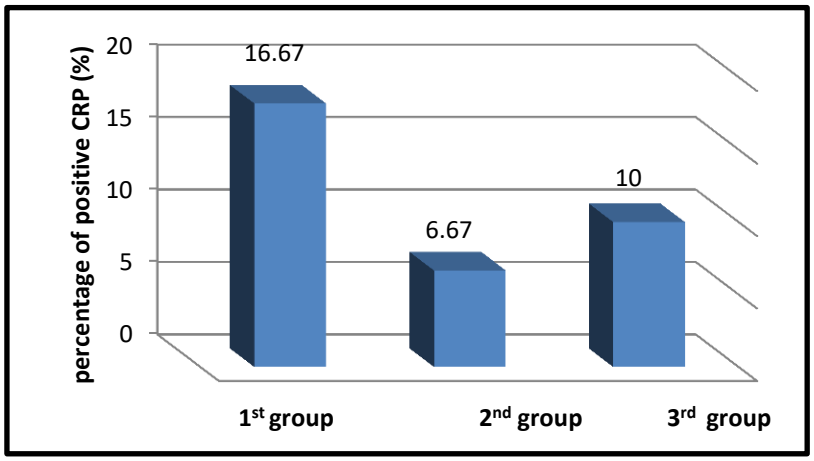

Figure 3: The effect of finasteride drug on the positive percentage of CRP in treated groups

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DISCUSSION

Total Prostate Specific Antigen (TPSA)

The normal value should be less than 4 ng/ml (Praveen, 2013) and a PSA level more than 1.5 ng/ml is recommended as a surrogate criterion for initiating therapy with 5α-reductase inhibitor (Sarma and John, 2012).

Elevated serum PSA levels in 1stgroup are probably aproduct of disruption of cellular architecture within the prostate gland, serum PSA is a reflection of epithelial cell volume, in that the more of these cells present, the higher the serum PSA. The loss of the barrier afforded by the basal layer and basement membranes within the normal gland is a likely site for the egress of PSA into the circulation (Mohammad, 2012; Jebor, et al. 2014). Our resultsagreewith, Al-saadi (2013) who observeda highly significant increased in BPH and BPH/LUTS patients ,elevate serum PSA level has an important marker of many prostate diseases including BPH, prostatitis, and PCa, however ,25%- 30% of the patients with clinically local disease will experience a clinical or a biochemical relapse i.e. increasing serum PSA level (D,Amico, et al. 2004). Decreased level of PSA in 2nd group due to finasteride affects .PSA in a highly predictable way cause a similar percentage reduction of about 50% (Guess, et al.,1993) , Guess, et al.(1993) reported that reduced PSA level by-41% at 6 months and at 12 months was -50%, similarity to results of(Kapoor,2012; Merck,2013; Magelan Medical Administration, 2015). Praveen (2013) reported the finasteride decreases PSA levels by 40-50%. Also, Hbib, et al. (1997) and Stanczyket al. (2013) reported in the finasteride treated group, PSA decreased from baseline to 1 month by 23.2%,the change in PSA decreased further to 46.1% and 55,1% at 3 and 12 month of treatment respectively.

Interleukin-17 (IL-17)

There were significantly differences among study groups that due to inflammatory infiltrates containing leucocytes associated with acute and chronic inflammation which is highly implicated in the BPH pathogenesis and progression (Nickel ,et al., 2008; Corona,et al., 2014; Q He, et al., 2016), also activated prostate-associated lymphoid tissue (PALT) stimulates the proliferation of other immuncompetent cells lead to an upregulation of several proinflammatorychemokines and cytokines (Corona, et al., 2014) .

Cytokines are important molecules responsible for inflammation secreted in response to tumors and often by tumor cells. Single nucleotide polymorphisms (SNPs) in promoter region of cytokine genes have been shown to alter the level of cytokines. Several polymorphisms in cytokines, both functional and nonfunctional have already been reported to have positive associations with prostatic growth (Kesarwani and Mittal, 2010) .

The inflammatory process is highly implicated in the pathogenesis of BPH and progression (Nickel, et al., 2008; Corona, et al., 2014). Inflammation is well established to be an amplificatory factor in prostate tumorigenesis (De Angulo ,et al. 2013), many studies have showed that the majority of lymphocytes in BPH tissue were T-lymphocytes, infiltration of chronically T lymphocytes and secretion of inflammatory cytokines with the prostatic gland are considered a determinant factor in BPH pathogenesis and progression (Fan, et al., 2014). . The most important potential cause for immune response in prostate is the prostatic microenvironment (Fibbi, et al., 2010). BPH epithelial cells, an important component of prostatic microenvironment, are suggested as a key role of the induction of immune-mediated inflammatory processes. On the other hand, intraprostatic DHT could affect function of epithelial cell directly (Fan ,et al., 2014). Our data are not consistent with a previous report of Vignozzi, et al. (2012) who highlighted that DHT exerts an immune regulatory role on human

prostatic stromal cells, inhibiting their potential to actively induce and/or sustain autoimmune and inflammatoryresponses. .Numasaki ,et al., (2003) reported that tumors with IL-17 grow more rapidly than controls in immunocompetent and irradiated mice, vascular elements of tumor tissues in IL-17 transfectants were significantly increased when compared with those of controls, suggest that IL-17 may accelerate in vivo tumor growth via acting as an angiogenic factor ,it is markedly promoted the development of microvessel-like structures ,therefore, IL-17 promotes angiogenesis via stimulation of vascular endothelial cell migration and cord formation. Steiner ,et al.(2003) reported the IL-17 expression was very weak and restricted to lymphocytes in normal prostate while in 79% of BPH specimens, the IL-17m RNA and protein expression was increased ,that could be shown for activated BPH-T cells suggest that IL-17 expression ,at least in prostate is not restricted to T-cell ,but is also expressed by BPH epithelial and smooth muscle cells.

The IL-17 level reduced in post-treatment group compared to pre-treatment group that due to effect of finasteride which resulted in reduced levels of systemic cytokines, this was accompanied by a reduced posttraumatic cytokine (Frink, et al. 2007), the finasteride administration prevented the increase in cytokine level, cytokine production normally observed after trauma was prevented by treatment with finasteride .

C-Rreactive Protein (CRP)

Increased percentage of CRP level (positive) in pre-treatment may be due to acute or chronic prostatic inflammation and might be related to the severity LUTS in BPH patients (Q He, et al., 2016) ,also may be due to induced by IL-6 which plays an important role in immune and acute-a phase inflammation responses and acute on hepatocytes to increase the synthesis of CRP and other acute phase reactant proteins (Chang, et al.2010).

Schenk, et al. (2010) demonstrated that circulating levels of inflammatory markers, include elevated CRP and IL-6 were associated with risk of incident, symptomatic BPH.

Rohrmann, et al. (2005) mentioned that men with a CRP level above the limit of detection (>3.00 mg/l) were 1.47 times more likely to have three or more BPH symptoms than men with a CRP concentration below the detection limit (not statistically significant).

CONCLUSION

The present study concluded to the BPH affects on some immunological parameters as PSA, IL-17, and CRP that increased significantly in BPH patients when compared to healthy. The 5-alph reductase inhibitor (finasteride) cause decreasing significantly in levels their, that meaning decreasing prostate volume and reduce in inflammation, thus reduce or ablation BPH severity.

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