Study of some biochemical and immunological parameters in Iraqi benign prostatic hyperplasia and lower urinary tract symptoms patients

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Key words Benign prostate hyperplasia, lower urinary tract symptoms Interleukin, hs-CRP, t-PSA, renal function test.

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Abstract

Benign prostatic hyperplasia (BPH) alone or with lower urinary tract symptoms (LUTS) was of the major public health problem among men especially over 55. In this trial serum interleukins six& eight (6&8) were estimated, also determining renal function test (urea& creatinine) and uric acid. Highly sensitive C- reactive protein (hs- CRP) and total prostate specific antigen (t- PSA) were measured in BPH, BPH+ LUTS and control groups. The result of this trial illustrate the elevation of all biochemical & immunological parameters significantly in both A&B groups when compared with control (P value= 0.002, 0.001 &0.000) except uric acid in group A appear insignificantly increased with group C (P value=0.477).

In conclusion the study predict the increasing in selected parameters very well & clearly so this help in diagnosis and management of BPH alone or with LUTS accompanies with inflammation which play an important role to transfer the benign disease to malignant. The aim of this study is to evaluate some clinical parameters especially hs- CRP that not previous used as a marker in the blood of elderly individuals who suffered from BPH with or without LUTS be of assistance in diagnosing & managing once in order to decrease the complication and severity of patient status which may convert the benign to malignant cases.

دراسة بعض القياسات البايوكيميائية والمناعية عند المرضى العراقيين المصابين بتضخم البروستات الحميد والاعراض المتعلقة باسفل الجهاز البولي

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مفتاح البحث :تضخم البروستات الحميد ، اعراض اسفل الجهاز البولي ،انترلوكين ، البروتين التفاعلي نوع ج ذو التحسس العالي ،المضاد الجيني للبروستات الكلي ، وظائف الكلى .

الخلاصه

تضخم البروستات الحميد لوحده او مع الأعراض المصاحبه له في أسفل القناة البوليه تعتبر مشكله عامه للرجال فوق سن الخامسه والخمسين. في هذه التجربة , تم قياس انترلوكين ستة وثمانية أضافة الى تعيين عمل الكليتين من خلال حساب مستويات اليوريا,حامض اليوريك والكرياتنين في مصل المرضى والأصحاء.أما مايحدد وجود أي نوع من الألتهابات فقد تم تحليل النماذج لمعرفة نسب البروتين التفاعلي نوع سي والعامل البروتيني المسمى بالمضاد الجيني للبروستات. أتضح من نتائج التجربة ان زيادة الدلائل الكيموحيوية والمناعية التي تم تحليلها وقياسها بشكل ملحوظ ومعنوي في مجموعتي المرضى (أ,ب)عند مقارنتها بالمجموعه (ج). (P value= 0.002, 0.001 &0.000) ، ماعدا ذلك فأن زيادة حامض اليوريك في مجموعه (أ) كانت غير معنويه عند مقارنتها بالاصحاء (ج) . (P value=0.477). نستنتج من هذه الدراسه ان الأزدياد الملحوظ والواضح لهذة العوامل أعلاه لها الفائدة الكبيرة عند التشخيص وكيفية التعامل مع مرض التضخم الحميد للبروستات فيما أذا كان لوحده أومصاحب لاعراض مرضيه أخرى في اسفل المجرى البولي مما قد تؤدي مستقبلا تحويله من حميد الى خبيث. الهدف من البحث هو تقييم بعض القياسات السريرية خاصة مستوى البروتين التفاعلي نوع ج ذو التحسس العالي الذي لم يستعمل سابقا كمعلم في دم المرضى المسنين الذين يعانون من تضخم البروستات الحميد مع الاعراض المرضية في اسفل الجهاز البولي أو بدونها التي تفيد في الكشف المبكر أضافة الى منع حصول المضاعفات وتعقيدها التي تبدل المرض من حالته الحميدة الى الخبيثة .

Introduction

Benign prostatic hyperplasia (BPH) is a well-known condition characterized by prostate growth accompanied by lower urinary tract symptoms (LUTS) [1, 2]. Both are highly prevalent& major conditions among older men [3, 4]. BPH appeared firstly as hypertrophy which is due to mechanical effect of congestion and enlargement of the prostate occurs and the pathological hydrostatic pressure in the testicular drainage systems is transmitted to the prostate via the testicular prostate drainage systems then followed by hyperplasia that included biological process of accelerated prostate [5].

Pathologically, BPH is due to cellular proliferation of the epithelial and stromal elements within the prostate gland. These changes, which begin histologically in the third decade of life and clinically in the fifth decade of life, are mediated primarily by tissue levels of dihydrotestosterone (DHT) within the prostate and result in its continued growth throughout life. When prostatic enlargement occurs, increased resistance in the proximal urethra may limit urinary flow during micturition, often resulting in pathophysiologic changes in the bladder wall. Consequently, LUTS due to prostatic obstruction are inseparable from symptoms due to bladder detrusor dysfunction [6, 7]. Clinically, BPH is distinguished by progressive development of LUTS and symptoms are variable that ranged from nocturia, incomplete emptying, urinary hesitancy, weak stream, frequency, and urgency to the development of acute urinary retention [8-10]. The traditional causal of BPH is hormones and genetic predisposition and modifiable risk factors are obesity, elevated fasting plasma glucose, cardiovascular disease, diabetes, dyslipidemia, and the metabolic syndrome may all significantly increase the risks of BPH and LUTS [11-16].

A number of cytokines and growth factors are involved in the process of immune dysregulation and chronic inflammation in BPH: those responsible for the permanent attraction of leukocytes and those that promote growth of prostate cells [17] although Kakehi *et al.* reported that patients with ‘‘symptomatic’’ BPH had down-regulation of the gene for macrophage inhibitory cytokine-1 (MIC-1), a cytokine with inhibitory effects on macrophage activity [18]. In vitro studies supported the role of inflammation, so stromal nodules of BPH present infiltrates of B lymphocytes, T lymphocytes, and macrophages .Those cells accumulate around the epithelial ducts and can disrupt glandular epithelium, the factors that trigger the infiltration are unknown, in contrast to normal prostate, quantitative RNA analysis reveals that BPH tissues show up to 3-fold higher interferon g (INF-g) levels and de novo expression of IL-4 and IL-2. Activated T cells represent the major source of cytokine production [19, 20]. Steiner *et al* studied the effect of interleukin 17 (IL- 17), a cytokine with a key pro inflammatory role, IL-17 is secreted by the activated CD4+ T cells and is able to stimulate epithelial, endothelial, and fibroblastic cells to produce several pro inflammatory molecules, such as interleukin one beta (IL-1b), tumor necrosis factor alpha (TNF-α), interleukin eight (IL-8), and cyclo oxygenase 2 (COX-2) [21]. Rohrmann *et al* studied the correlation between prostatic hyperplasia and C-reactive protein, a nonspecific marker of inflammation [22].

For detection renal function, It is well-accepted today that bladder outlet obstruction due to BPH might cause hydronephrosis and renal failure .Most studies have found that the incidence of azotaemia in men with BPH varies from 15-30% [23, 24].

Prostate-specific antigen (PSA) is a glycoprotein produced by prostate gland as a marker for prostate cancer, benign prostate hyperplasia and prostatitis. PSA is one of the major proteins in seminal fluid with concentrations of 0.2 to 3.0 mg/ml. Its main function is to liquefy the seminal fluid [17, 25- 27]. The aim of revision is to evaluate some clinical parameters especially hs- CRP & t-PSA as potent markers in elderly individual’s blood who suffered from BPH alone or with

LUTS be of assistance in diagnosing & managing immediately in order to decrease the difficulty and severity of patient status which may convert the benign to malignant cases& increasing the mortality.

Materials& Methods

Forty four out patients with BPH and BPH with LUTS attending the department of internal medicine (Urology) Al- Cindy Hospital were selected to participate in this study compared with fifteen aged – matched healthy male as control. Their mean ages ± standard deviation of mean in those 3 groups were (66.8± 5.23), (67.1± 3.32), (63.98± 4.09) years.

These patients were selected with some clinical and biological information for each patient was provided by indicating the age of the patient, weight, height. Patients who suffered from cardiac diseases, diabetes, hypertension, dyslipidemia, smokers, alcoholism, active acute infections and metabolic disorders were excluded.

Seven questions related to the symptom included:

Incomplete emptying, frequency, intermittency, urgency**,** weak stream, straining and nocturia . All patients were diagnosed according to international prostate symptoms scores (IPSS) [(28)].

Blood samples were collected from all subjects (disease& healthy). Diseased individuals undergoing per rectal examination and ultrasound of the prostate .The trial was done under super vision of urologist in the urological department.

Table (1): indicate the correlation between the studied groups & many factors.

Individuals were divided into 3 groups:

1- Group (A): Twenty four patients who suffered from BPH only.
2- Group (B): Twenty patients who have both BPH+ LUTS.
3- Group (C): Fifteen volunteers as control (healthy).

Ten milliliters of venous blood were draw in plain centrifuge tube in order to get the serum and discard the precipitate then keep all samples in deep freezing – 20 C° till the time of analysis.

Body mass index (BMI) was calculated by measuring the weight in (Kilogram) & height in (meter); dividing the weight over the square height to assess BMI which provides a reliable indicator of body fatness [(29)].

BMI (Kg/ m^2) Categories:

Underweight = <18.5
Normal weight = 18.5–24.9
Overweight = 25–29.9
Obesity = BMI of 30 or greater

IPSS: International Prostate Symptoms Score

Mild scores = 0-7
Moderate scores = 8-19
Sever scores = 20-25

Total PSA, highly sensitive C reactive protein (hs CRP)/ DRG- Germany, interleukin six& eight (IL 6&8) kits were purchased from Bio Source/ Europe, were measured by enzyme linked immune sorbent assay ELISA technique [Bio ELISA reader (Biotech)] [(30)].

Creatinine, uric acid & urea were detected by enzymatic kits (Randox Company, UK.) and measured by spectrophotometer (Cecil/ England). The Jaffe reaction is a colorimetric method used in clinical chemistry to determine creatinine levels in blood and urine. Creatinine reacts with picric acid in alkaline media such as sodium hydroxide solution (NaOH), and formed a

reddish-orange color called creatinine picrate[31]. Uric acid was assessed by Gj0rup *et al.* enzymatic method [32] depending conversion of uric acid to allanton by uricase. Urease librates ammonia which reacts with Berthelot phenate – hypochlorite colored complex compound [33].

Statistical calculation is done according to paired t-test. P value<0.01 indicate significant. The analysis of data is estimated by using SPSS program version 18.

Results

Figure (1) and tables (2&3): The first three columns show the comparison between BPH and control groups. Urea, hs CRP, IL-6&IL-8 with t PSA increased extremely and in very high significant P value= 0.000 in serum of the patients in group (A) while creatinine P value= 0.002 is prominent in lesser extent than above parameters but also be significant. Only uric acid appear to be insignificant increments P value= 0.477.

Figure (2) and tables (2&3): The second three columns confirm the comparison between BPH+LUTS and control groups. Serum values of urea, creatinine, uric acid, hs CRP, IL6&8 and t PSA registered greater level than in control, P value= 0.000 highly significant.

Figure (3) and tables (2&3): The last three columns confirm the comparison between BPH and BPH+LUTS groups. Serum values of urea, creatinine, uric acid, hs CRP, IL6&8 and t PSA registered greater level group (B)than in (A) , P value= 0.000 highly significant.

Discussion

The study demonstrate the effects of BPH with/ without LUTS on renal function test when compared with control by increasing significantly both serum urea and creatinine level as well as uric acid but at lesser extent (table2, figures 1,2&3). This observation is agreement with previous studies especially with measurement of blood creatinine level so many different factors influenced the function of renal system like age throughout their lives, men produce both testosterone, an important male hormone, and small amounts of estrogen a female hormone. In ageing: the amount of active testosterone in the blood decreases, leaving a higher proportion of estrogen this fact may suggest that BPH occur because the higher amount of estrogen within the gland increases the activity of substances that promote cell growth. Another theory focuses on dihydrotestosterone (DHT), a substance derived from testosterone in the prostate, which may help control its growth. Prior study used animals in order to detect lose their ability to produce DHT as they age. However, some research has indicated that even with a drop in the blood's testosterone level, older men continue to produce and accumulate high levels of DHT in the prostate. This accumulation of DHT may encourage the growth of cells. Scientists have also noted that men who do not produce DHT do not develop BPH. In chronic BPH can cause urine to back up into the kidneys and damage them [8, 10]. Lower urinary tract symptoms (LUTS) possibly related to benign prostatic enlargement (BPE) and benign prostatic obstruction (BPO) due to BPH interfere significantly with normal daily activities [34, 35, 36]. It is well-accepted today that bladder outlet obstruction due to BPH might cause hydronephrosis and renal failure [23, 24]. Comiter *et al.* [37] reported a study in which voiding dysfunction of a non- neurogenic etiology did not appear to be a risk factor for elevated BUN (blood urea/nitrogen) and creatinine levels.

Previous study showed a much higher mortality among BPH patients who underwent surgical treatment when renal insufficiency was present at the same time. Patients with BPH also have a significantly higher risk of chronic kidney disease, probably due to an obstructive uropathy. Chronic kidney disease has been consistently proved to be a significant risk factor for bladder cancer in the population [38, 39, 40, 41].Serum level of interleukins (IL-6&8) and hs- CRP is increased at high significant values in both diseased groups (tables 2, 3& figures1, 2& 3). The results have many explanations that include systemic and local hormonal and vascular alterations as well as prostatic inflammation that would stimulate cellular proliferation [1]. Prostate has ability to remodeling its tissues during the life related with age, so the growth in volume estimated as medium 0.6 ml per year of age, corresponding to a median growth rate of 2.5% per year [42].

Roberts *et al* studied the hormonal alteration and reported higher intracellular metabolite of testosterone, dihydrotestosterone (DHT) activity in BPH relative to normal prostate gland tissue [43,44] resulting as a permissive, rather than a transformative, mediator in the development of BPH. Also the prostate is normally populated by small numbers of T cells, B lymphocytes, macrophages, and mast cells [45, 46]. Interestingly, several studies showed that the prostatic tissue in BPH patients contains a disseminated infiltration of T and B lymphocytes and numerous colonies of macrophages [45,47].Other study demonstrated that IL-17 up-regulated the secretion of other pro inflammatory cytokines, such as IL-8 and IL-6 by stromal cells, these interleukins are recognize as two potent growth factors for prostatic epithelial and stromal cells.IL-8 playing a major role in stromal proliferation by the induction of fibroblast growth factor- two (FGF-2) [21]. Numerous authors proved that adipokines produced by human white adipose tissues (WAT), interleukin-6 is one of them and its secretion might represent 10-30% of circulating levels. Plasma IL-6 is highly correlated with body mass and inversely related to insulin sensitivity [48-51].This fact proved that group (A&B) in present trial had overweight BMI (table 1) and their IL-6 serum level increase at significant value (table 3).

Hs-C reactive protein (hs CRP) illustrate significantly increase in the serum of all patients. This type of protein detects in cardiovascular disease previously [52]. CRP is common; its normal concentration in healthy human serum is usually lower than 10 mg/L, slightly increasing with aging. Higher levels are found in late pregnant women, mild inflammation and viral infections (10–40 mg/L), active inflammation, bacterial infection (40–200 mg/L), severe bacterial infections and burns (>200 mg/L) [53]. Rohrmann et al. illustrated the correlation between prostatic hyperplasia and C-reactive protein, a nonspecific marker of inflammation in a cross-sectional study on a sample of the US civilian, non institutionalized population, collecting structured interviews concerning LUTS, a physical examination, and C reactive protein measurements in 2337 men. The data were not statistically significant increased , they might suggest a trend for a correlation between LUTS and C-reactive protein and support further research in the period of serum biomarkers inflammation in BPH [22]. CRP levels rise rapidly during acute inflammation and elevated levels are also a marker for chronic inflammation [54].

A number of characteristics have been found to be associated with elevated CRP levels, such characteristics may have explained the associations observed between CRP levels and BPH/LUTS outcomes. In particular, body mass index has been strongly associated with elevated CRP levels, whereas weight loss has been associated with a decline in it [55-59].

Total prostate specific antigen serum level (t PSA) shows a highly significant elevation in BPH & BPH+ LUTS in this study (table 3& figures 1, 2, 3).

Elevated serum PSA level has become an important marker of many prostate diseases including benign prostatic hyperplasia, prostatitis, and prostate cancer [60, 61].

However, 25% to 30% of the patients with clinically local disease will experience a clinical or a biochemical relapse, i.e. increasing PSA levels in serum [62].

Table (1) assessed BMI of diseased groups (A&B) proceedings over weight comparing with control and this result have the same opinion of many studies.

Lagiou *et al* dictated that there is a positive association of BPH risk with diet such as butter, margarine and seed oils which can increase serum cholesterol levels [63]. Adlercreutz H. [64] explains this relation according to the idea of high fat diet causes an elevation of plasma testosterone level and might be associated with BPH. While others suggested their theory on accompanied between BPH (prostate growth) and abnormal lipid metabolism [65] and Hammarsten *et al* examined (158) patients with BPH and found a statistically significant relation between BPH and low HDL /cholesterol ratio [66]. Obesity and diabetes are also associated with systemic inflammation and oxidative stress, which may promote the inflammatory processes in the prostate, leading to clinical development of BPH [67].

Conclusion

The trial observes several findings that play an important role in prognosis& pathophysiology of BPH either alone or with LUTS. Furthermore; over weight of both diseased groups also play a chief role in initiation, prediction the inflammatory processes and their markers that finally increase the complication and raise mortality.

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Table (1): Demographic data of BPH, BPH+ LUTS & control groups

character		BPH= A	BPH+LUTS= B	Control= C
No. of individuals Male		24	20	15
Age (year)		67.1 ± 3.32	63.98± 4.0 9	66.8± 5.23
Body mass index		25.15± 1.97	29.71±1.03	22.99± 1.21
IPSS	Mild	6 (25%)	2 (10%)	
	Moderate	10 (41.66%)	3 (15%)	
	Sever	8 (33.3%)	15 (75%)	

Table (2): Show serum level (mean ± standard deviation of mean) of urea, creatinine& uric acid measured in milligram per deciliter (mg/ dl) while hs C reactive protein (hs CRP) measured in milligram per liter (mg/L) in BPH= (A), BPH+LUTS= (B) and control= (C) groups. P value was calculated between each two different groups that shared in this study. P = 0.001- 0.002(*) mean highly significance value & P= 0.000 (**) is very high significant.

Parameters		(A)	(B)	(C)	P value (A&B)	P value (A&C)	P value (B&C)
Urea	mg/ dl	56.93±4.59	61.39±3.23	50.77±5.26	0.001*	0.000**	0.000**
Creatinine		1.26± 0.22	1.56±0.18	1.05±0.144	0.000*	0.002*	0.000**
Uric acid		4.68±0.48	6.79±0.36	4.56± 0.47	0.000*	0.477	0.000**
High sensitive C reactive Protein	mg/L	5.004±0.362	10.04±1.58	2.803±0.502	0.000*	0.000**	0.000**

Table (3): Show serum level (mean ± standard deviation of mean) of interleukin six& eight (IL-6& 8) total prostate specific antigen (t PSA), they were measured in picogram per milliliter (pg / ml) and nanogram per milliliter (ηg /ml) respectively in A,B & C groups with their P values for all result appear to be very high significant (**).

Parameters		(A)	(B)	(C)	P value (A&B)	P value (A&C)	P value (B&C)
IL-6	pg/ml	14.56±1.104	8.82±0.929	12.6±0.82	0.000**	0.000**	0.000**
IL-8		5.21±0.677	2.702±0.631	4.307±0.414	0.000**	0.000**	0.000**
Total PSA	ηg/ml	6.05±0.725	6.05±0.725	4.176±0.548	0.000**	0.000**	0.000**

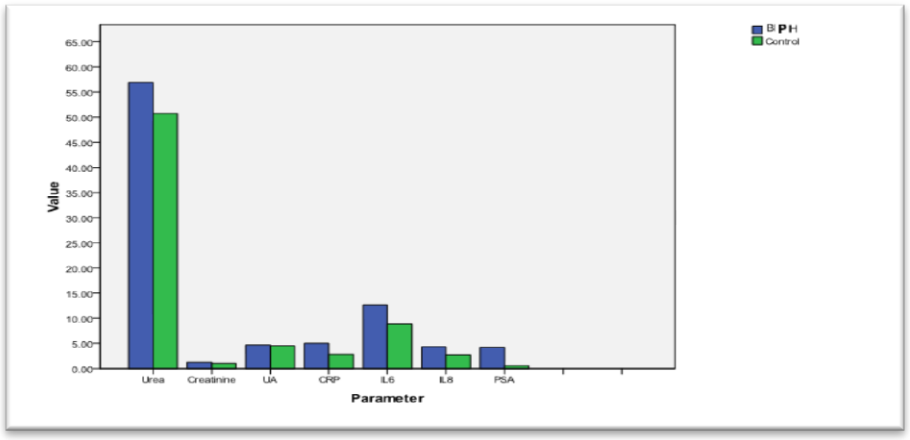

Figure (1): Demonstrate the mean value of urea, creatinine, uric acid, hs CRP, IL-6, IL-8 and t PSA in the serum of both BPH and control groups.

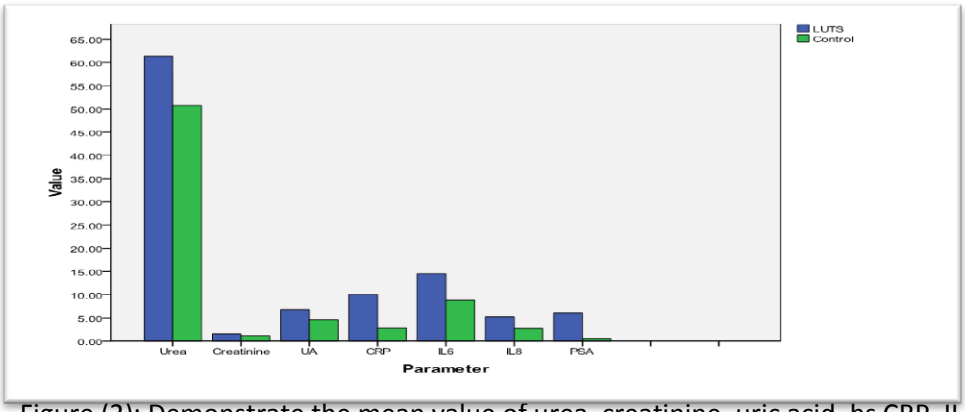

Figure (2): Demonstrate the mean value of urea, creatinine, uric acid, hs CRP, IL-6, IL-8 and t PSA in the serum of both BPH+ LUTS and control groups.

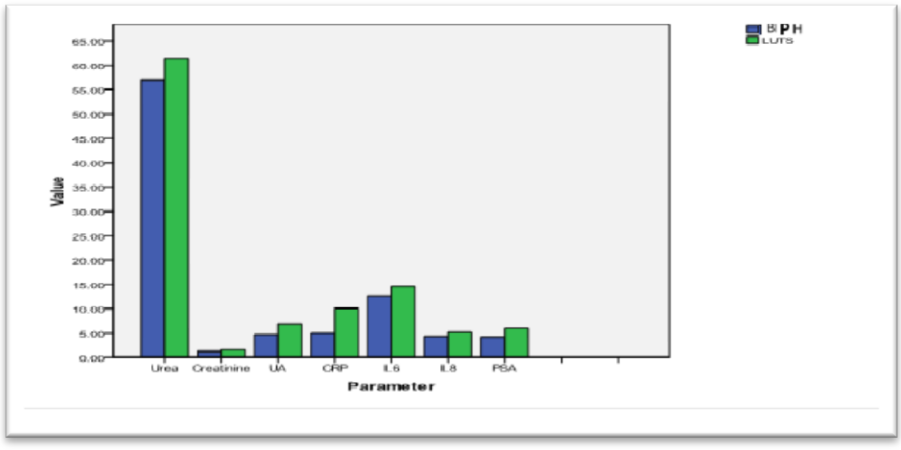

Figure (3): Demonstrate the mean value of urea, creatinine, uric acid, hs CRP, IL-6, IL-8 and t PSA in the serum of both BPH and BPH+ LUTS groups.