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Estimation levels of prostate-specific antigen, interleukin-8, oxidative stress and some inflammatory markers in sera of benign prostatic hyperplasia patients who have smoking habits as a risk factor

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Abstract: Benign prostatic hyperplasia (BPH) is a common multifactorial inflammatory disease of older men, defined by increased growth of prostate epithelial and stromal cells. Elevation serum levels of Interleukin-8 (IL-8), oxidative stress and inflammatory markers represent predictive surrogate markers of the disease progression in smoker BPH patients. A total of 86 BPH patients and 54 control subjects were admitted to the urology unit, Rizgary Teaching Hospital in Erbil City, Iraq between January and June 2020. Sera levels of prostate-specific antigen(PSA), IL-8, malondialdehyde (MDA), high sensitive C-reactive protein (hs-CRP), testosterone and some biomarkers concentrations were measured in the patients according to instructions of manufacturers. Patients and controls were categorized into groups according to smoking status (smokers and non-smokers). The sera levels of PSA, IL-8 and inflammatory markers like oxidative stress(MDA), hs-CRP and testosterone in every smoker subgroup (BPH patients and control) increased compared to the same non-smoker subgroups and significantly increased compared with non-smoker control ($p<0.05$). PSA demonstrated a significant positive correlation with the following terms, IL-8, MDA, hs-CRP, testosterone and low-density lipid (LDL)($p<0.05$) and, insignificant negative correlation with high-density lipoprotein(HDL), ($p>0.05$). The current study demonstrated mounting evidence to support the role of smoking in the pathophysiology of BPH through elevation levels of inflammatory and oxidative stress biomarkers in sera of BPH patients.

Key words: Benign prostate hyperplasia; Interleukin; Oxidative stress; Smoking.

Introduction

Benign prostatic hyperplasia (BPH) is a term used for describing benign histological patterns according to the American Urological Association (AUA) and the European Association of Urology (EAU) (1). It is a progressive disease of aging males that affecting their life quality, and lower urinary symptoms represent one of their complications (2,3). BPH is a multifactorial disease in which age, inflammation, genetics, obesity, hormones, metabolic syndrome and lifestyle are potential factors related to the development of the disease (4). Prostate-specific antigen (PSA) as a sensitive glycoprotein marker, used for diagnosis prostate hypertrophy and cancer (5). This marker present normally at low levels in the blood with reference range less than 4 ng/mL (6), and more than 4 ng/mL in BPH progresses, prostatitis and prostate cancer(7). BPH also engaged by a pro-inflammatory cytokine, interleukin 8 (IL-8) as one of CXC chemokine, that induce inflammation by the production of several inflammatory cytokines and chemokines besides chemoattraction of inflammatory cells (8). Additionally, the pathogenesis of BPH is possibly triggered by many other factors, such as oxidative stress(OS) (9), and hormonal status like androgens (testosterone and dihydrotestosterone), they play a vital role in proliferation and survival of prostatic cells (10). Cigarette smoke contained many oxidants and pro-oxidants compounds capable of producing reactive oxidative stress (ROS) (11). ROS, represent an imbalance between oxidant and antioxidant molecules, in favor of oxidants, that may cause different diseases involving BPH (12). The risk of hyperplasia increased with recurred tissue damage and oxidative stress (OS)may prompt cellular proliferation (13). The crucial origin of free radicals that can stimulate prostate hyperplasia through OS is implicated by macrophages and neutrophil supply infiltration (14). Malondialdehyde(MDA), as the final product of lipid peroxidation, is utilized as a non-invasive biomarker of OS and acts as an index of lipoperoxidation involved in both recent and chronic damages of prostate tissue and their pathophysiological conditions (12,15). Furthermore, aging and OS are the common risk factors for BPH and prostate cancer (16). OS can produce genomic and vascular damage that is involved in DNA repair and apoptosis. Cigarette smoking can lead to OS for both direct smoker and indirect smoker because it has hundreds of potentially toxic components with multiple actions in the human body (17). Additionally, both phases of cigarette smoke, particulate and gaseous, contain extremely high concentrations of free radicals 18). As far as we know, limited data exist about the relationship between inflammatory markers like PSA, IL-8, oxidative stress, CRP and BPH in the presence of smoking habit as a risk factor. The present study aims to investigate serum levels of PSA, IL-8, MDA, and other inflammatory

markers in order to clarify the impact of inflammation and oxidative stress in BPH patients in the presence of smoking habit as a risk factor. Furthermore, to the best of our knowledge, this is the first study in our region evaluating the diagnostic values of PSA, IL-8, MDA and CRP levels in BPH smoker patients. Moreover, the study investigated whether a correlation exists between serum levels of the above inflammatory parameters in BPH patients.

Materials and Methods

This case-control study was carried out between January and June 2020 in which 86 newly diagnosed male with ultrasound and biopsy-confirmed BPH and 54 apparently healthy age-matched males as a control were enrolled. Inclusion criteria included diagnosed patients for BPH upon clinical examination by urologists in Rizgary Teaching Hospital in Erbil City, Iraq, however patients, who were diagnosed with prostate carcinoma or with any evidence of autoimmune and who were taking drugs for prostatic hyperplasia were excluded from the study. All BPH patients had enlarged prostate with elevation in PSA level (more than 4ng/dl), however, the control group, had no prostate enlargement, nor elevation in PSA level (less than 4ng/dl)). The sera from participants were examined by the following laboratory investigations PSA, IL-8, MDA, hsCRP, hormonal status like testosterone, prolactin, FSH and LH, kidney function tests like urea, creatinine and uric acid. Furthermore, low-density lipid(LDL) and high-density lipid (HDL) were also measured as lipid profile tests. Tests were performed according to the instructions of manufacturers.

This study was approved at the College of Medicine, Hawler Medical University by the medical ethics committee. Medical history information was obtained during personal interviews using formatted questionnaires. Serum PSA concentration was measured by using a two-step enzyme immunoassay sandwich method with a final fluorescent detection, Enzyme-Linked Fluorescent Assay (ELFA)(Minivdas, France), results are automatically calculated by VIDAS to show PSA concentration in ng/dl, hence PSA less than 4 ng/dl represents a normal level in the blood. The serum IL-8 level was estimated quantitatively using enzyme-linked immunosorbent assay (ELISA) (Komabiotech, Korea), Serum MDA level was measured quantitatively using the human MDA spectrophotometer kit (Northwest, Canada). The quantitative estimation of hs-CRP serum level was performed using Cobas 111(Roche Diagnostics GmbH, Germany), however, the miniVIDAS technique was used for detection serum hormones level (Minivdas, France). Lipid profiles and HbA1c were analyzed using cobasc111 (Roche Diagnostics GmbH, Germany). Body mass index was calculated depending on the standard equation according to WHO criteria (weight Kg / height m^2) (19).

The study protocol was approved by the medical ethics committee of the College of Medicine/ Hawler Medical University. Baseline information was obtained through a direct personal interview with all participants using a prepared questionnaire format. Approximately 8 ml of the venous blood sample was obtained from each patient and control subjects. Obtained serum was kept in many aliquot tubes, and stored at -80°C for further investigations. The collected data were analyzed using computer program software, statistical package for social sciences (SPSS) version 23.0. The continuous variables of studied groups were described as mean ±SE using a one-way analysis of variance (ANOVA). □□wo continuous variables be compared by Student's *t*-test. Chi-squared test (χ^2) was performed for categorical variables. The linear relationship between every two variables was analyzed by the Pearson correlation coefficient test. Results were considered significant if the P-value was less than 0.05.

Results

Table (1) shows the baseline information of study groups (BPH patients and controls). The patients revealed higher mean age (58.78, ranged between 30-83 years) compared to control (50.78, ranged between 19-82 years), and showed a significant difference ($p<0.05$). Levels of inflammatory markers like PSA, IL-8, MDA, hsCRP, and WBC, were also showed significant elevation in BPH patients ($p<0.05$) compared to control group, meanwhile, LDL level observed insignificant elevation in patients compared to control($p>0.05$), however, the inverse result was observed regarding HDL level (insignificant decrease) ($p>0.05$). Similar results were observed for BMI, HPA1c, family history ($p>0.05$) (Table 1). The kidney function test revealed a significant increase in uric acid level in BPH patients compared to control ($p<0.05$), meanwhile, no statistically significant differences were observed for urea and creatinine levels ($p>0.05$). Hormonal status revealed the significant increase in testosterone levels in BPH patients compared to control ($p<0.05$), and no statistically significant differences were observed for prolactin, LH and FSH levels ($p>0.05$).

Additionally, BPH patients represented significantly higher percentages of some risk factors like a smoker, and obese (55.81% and 46.51% respectively) compared to the control group ($p<0.05$). Diabetic Mellitus and hypertension revealed a higher proportion of BPH patients (45.34%, and 40.69% successively) with no statistically significant difference among the groups ($p>0.05$). Illiterate, Married, and self-employed individuals have represented the higher percentages in BPH patients compared to control groups with a non-significant difference ($p>0.05$).

Table 2 describes a comparison of the levels of some inflammatory markers like IL- 8, MDA and other inflammatory markers, lipid profile, hormonal status and kidney function test between BPH patients and control group in regard to smoking as a risk factor. Smokers BPH patients were older and had higher BMI compared to non-smoker patients and the significant difference was observed for BMI ($P<0.05$). Additionally, smokers' control showed a non-significant higher BMI compared to non-smoker controls ($P>0.05$). Regarding the PSA level, smoker BMI showed a higher PSA level than other study groups, with a statistically significant difference compared to smokers and non-smokers control subgroups ($p<0.05$). IL-8 and MDA levels were significantly increased in smokers BPH patients compared to

Table 1. Socio-demographic characteristics and serum levels of parameters of the study groups.

Variables	BPH patients No.86	Control No.54	p
Age(years)	58.78±2.35	50.78±2.59	0.042
Age range	(30-83)year	(19-82) years	-
BMI (kg/m²)	26.63±0.99	25.40±0.69	0.524
HPA1c(mg/l)	6.34±0.38	5.53±0.12	0.061
Family history of BPH: No (%)	23(27.90)	12(22.22)	0.548
Inflammatory biomarkers			
PSA(mg/L)	9.04±0.74	1.40±0.20	0.001
IL-8(pg/ml)	346.32±13.35	205.08±8.93	0.001
MDA(µMµmol/l)	0.46±0.03	0.23±0.06	0.025
hsCRP(mg/L)	8.52±1.30	2.44±0.25	0.001
WBC(103/µL)	9.72±0.42	7.25±0.35	0.001
LDL(mg/dl)	89.37±1.84	86±0.77	0.542
HDL(mg/dl)	43.48±0.95	49.78±0.87	0.241
Kidney function test			
Urea(ng/ml)	42.51± 5.14	37.55 ±2.42	0.382
Creatinine(mg/dl)	1.07± 0.07	1.03± 0.04	0.672
Uric acid	32.89± 6.94	5.54± 0.21	0.001
Hormone status			
Testosterone	1.42 ±0.22	2.81± 0.11	0.012
Prolactin	13.42±1.07	15.82±1.08	0.093
LH	**3.04± 0.49**	4.48 ±1.09	0.164
FSH	3.97±0.65	6.51±2.03	0.257
Risk factors No (%)			
Smokers	48(55.81)	25(46.29)	0.042
Obese	40(46.51)	19(35.18)	0.000
DM	39(45.34)	21(38.88)	0.452
Hypertension	35(40.69)	20(37.03)	0.661
Education Levels			
Illiterate	30(34.88)	18(33.33)	0.792
Primary + secondary	26(32.55)	23(42.59)	0.136
High School and above	**20(23.26)**	**13(24.07)**	0.912
Marital status			
Single	7(8.13)	2(3.70)	0.298
Married	74(86.04)	45(83.33)	0.662
Widowed / divorce	9(13.77)	3(5.55)	0.222
Occupation			
Public sector	16(18.60)	8(14.81)	0.532
Private sector	58(67.44)	37(68.51)	0.894
Retired	12(13.95)	9(16.66)	0.305

Data are presented mean ± SE and as number (%). Body mass index: BMI; HPA1c:Hemoglobin A1c; IL-8: Interleukin-8; MDA: Malondialdehyde; PSA: Prostate specific antigen; hsCRP: high sensitivity C reactive protein; WBC; White blood cells; LH: Luteinizing hormone; FSH: Follicle stimulating hormone; DHL-C: high density lipoprotein-cholesterol; LDL-c; LDL: low density lipoprotein-cholesterol.

non-smokers patients and control subgroups. Similarly, hsCRP and WBC observed the same results when compared with non-Smokers control ($p<0.05$). Although the LDL level was higher, and the HDL level was lower in smoker patients, the differences were insignificant compared to other study groups ($p>0.05$). The level of prolactin was higher in BPH compared with study groups and the significant difference was observed with non-Smokers control ($p<0.05$). Conversely, the mean concentration of testosterone showed a lower value in smoker BPH and the difference was statistically significant compared to smoker and non-smoker controls ($p<0.05$). The levels of FSH and LH were also decreased in BPH patients compared with other study groups without a statistically significant difference ($p<0.05$), table 2. Finally, regarding kidney function test results, urea level was higher in smoker BPH patients compared with study groups and the significant difference was observed with control subgroups ($p<0.05$), meanwhile creatinine and uric acid levels non significantly increased in

Table 2. Comparison of IL-8, MDA levels and other inflammatory markers, lipid profile, hormonal status and kidney function test between BPH patients and control group in regard to smoking.

Variables	PBH Patients No.86		Controls No.54		P-value
	Smoking (n = 48)	Non-smoking (n= 38)	Smoking (n = 25)	Non-smoking (n = 29)	
Age (year)	59.23±3.82[a]	55.06±3.25[a]	50.10±2.85[a]	55.29±4.47[a]	0.27
BMI (kg/m²)	28.81±1.28[a]	21.93±0.73[c]	27.33±0.93[ca]	25.01±0,96[c]	0.038
HBA1c(mg/l)	5.89±0.84[a]	5.25±1.20[a]	3.94±1.14[a]	3.50±0.64[a]	0.345
Inflammatory Markers					
PSA(mg/dl)	10.96±1.74[ab]	9.76±1.21[b]	1.79±0.25[c]	0.81±0.27[c]	0.001
IL-8(pg/ml)	386.86±6.23[a]	313.89±5.17[b]	313.89±5.17[c]	214.66±7.30[d]	0.001
MDA(µM/L)	5.98±0.43[a]	4.79±0.53[b]	2.16±0.18[c]	1.73±0.05[c]	0.001
hsCRP(mg/L)	8.78±3.93[a]	6.99±1.47[ac]	2.18±0.53[bc]	1.07±0.25[c]	0.012
WBC(10^3/µL)	9.93±0.59[ab]	9.42±0.75[b]	7.79±0.39[c]	6.49±0.54[c]	0.013
Lipid profile					
LDL(mg/dl)	96.77±13.24[a]	87.94±4..45[a]	85.14±6.23[a]	84.61±9.14[a]	0.856
HDL(mg/dl)	41.29±1.57[a]	46.70±5.68[ab]	47.63±4.71[ab]	51.83±2.99[b]	0.213
Hormone status					
Testosterone(ng/ml)	1.89±0.20[ab]	2.31±0.11[cb]	2.19±0.11[b]	2.72±0.30[c]	0.034
Prolactin	16.36±1.17[ab]	16.32±1.70[cb]	14.18±1.89[ca]	11.94±0.82[c]	0.143
FSH	4.11±0.62[a]	3.92±0.43[a]	4.25±1.47[a]	5.22±1.40[a]	0.758
LH	3.02±0.41[a]	3.09±0.49[a]	3.38±1.05[a]	3.3±0.85[a]	0.971
Kidney function test					
Creatinine	1.16±0.13[a]	1.05±0.23[a]	1.04±0.07[a]	1.06±0.10[a]	0.775
Urea	48.12±8.83[a]	35.61±3.19[ab]	35.05±2.63[b]	33.21±2.22[b]	0.147
Uric acid	5.94±0.49[a]	5.90±0.38[a]	5.50±0.33[a]	5.19±0.24[a]	0.431

Values are presented as mean ± SE using F test, p values <0.05 considered statistically significant.

Table 3. Correlation between PSA, IL-8, MDA and different other inflammatory factors in begin prostatic hyperplasia patients.

Variables	PSA		IL 8		MDA	
	r	P	r	P	r	P
PSA	-	-	0.614	0.000*	0.923	0.000*
MDA	0.923	0.000*	0.298	0.245	-	-
CRP	0.947	0.000*	0.268	0.298	0.704	0.002*
WBC	0.174	0.040*	0.505	0.039*	0.261	0.31
HDL	-0.737	0.000*	-0.0668	0.800	-0.224	0.387
LDL	0.749	0.000*	0.420	0.119	0.150	0.593

r: Pearson correlation, p: p value, *p<0.05: Significant, **p<0.01: Highly significant, p>0.05: Non-significant.

the above-mentioned study group(p>0.05) table 2.

Pearson correlation analysis showed a significant positive correlation between PSA and study inflammatory parameters, IL-8, MDA, CRP, WBC and LDL(p<0.05), meanwhile significant negative correlation with HDL(p<0.05). Significant positive correlation was also observed regarding IL-8 with WBC (r=0.505, p=0.039) and MDA with CRP (r=0.704; p=0.002). Meanwhile, an insignificant negative correlation was observed between HDL and both inflammatory markers IL-8 (r=-0.0668, p=0.800) and MDA (r= -0.224, p=0.387), table 3.

Discussion

The BPH patients in the present study were older and had more BMI than control, the finding obtained in the current study were similar to those of Kucukdurmaz et al., who revealed that BPH and prostate cancer are diseases of aging men and associated with increased oxidative stress (20). Moreover, a study had identified obesity as a risk factor for BPH associated inflammation (21). The Reactive Oxygen Species (ROS) are produced in intense amounts with the progress of age that causes extensive damage to a different organ in the body under oxidative stress and may be related to the pathogenesis of BPH (22). The mean serum levels of inflammatory markers also increased significantly in BPH patients compared to the control group, this finding is in agreement with past researches for each of the following inflammatory terms, IL-8 (23-25), PSA (26), MDA (27-29) and hs-CRP (30).

Clinical studies suggested a potentially important role of chronic inflammation in BPH pathogenesis. Interleukin IL-8 represent the most important cytokine involved in the development of BPH, it has a direct effect on epithelial and stromal proliferation by produc-

tion various chemokines like CXC group that attract immune system cells within the prostate tissue. The attracted inflammatory cells produce many cytokines that stimulate the production of chemokines by stromal cells and responsible for prostate cell proliferation and the development of BPH (31,32). Patient with BPH with elevated IL-8 level, their stroma is essentially different from the normal prostate stroma. This reactive stroma pattern in BPH correlated with IL-8 elevation in the adjacent epithelium (24). Dysregulation of the immune response in BPH may occur via elevated expression of proinflammatory cytokine-like IL-17, which stimulates a hyperproduction of IL-6 and IL-8, key executors of stromal growth in BPH (33). Furthermore, increased levels of IL-8 in BPH tissues enhance the induction of a potent stromal growth factor (34).

The OS may occur if the amount of free radicals increases and antioxidants decrease (11). The relationship between OS and BPH has been estimated in several articles with conflicting results. Savas et al. revealed no significant OS differences between men with BPH and a control group (35). In contrast, Aydin et al. demonstrated an increased MDA level in men with BPH (36). Moreover, Gecit et al. declared that men with BPH had a higher OS when compared to control subjects (37). The significantly increased serum MDA level in BPH patients as a marker of oxidative stress is indicative of excessive lipid peroxidation in the BPH patients and indicates the imbalance between pro-oxidants and antioxidants status in favor of pro-oxidants (22). As a result, the elevation of MDA, inflammatory parameters and LDL level with a concomitant low level of HDL in serum is obtained in the present study. Since the prostate tissue is subject to OS damage due to rapid cell turnover and fewer DNA repairing mechanisms, those events may result in a genetic variation like point mutations, deletions or rearrangements which may contribute to either benign hyperplasia or prostate cancer (13). Moreover, The serum CRP level in the present study increased in BPH patients than control and smoker group as well, this result in line with a study demonstrated that serum CRP levels in men with BPH and LUTS increased with age, higher PSA levels and the increased severity of LUTS (38). The serum CRP level is considered as the surrogate of chronic inflammation (38).

Smoking subjects in both groups patients and control revealed significant increases in MDA level compared with non-smoking subjects in the present study, this elevation was previously observed in smoking healthy compared with non-smoking subjects (39). This result suggesting that they have been exposed to more oxidant stress than non-smoking subjects group. The proinflammatory properties of cigarette smoke are well documented (40). Various studies have shown that smoking stimulates lipid peroxidation by enhancing the MDA level (41). A chemically various substance of pro-inflammatory, oxidative and carcinogenic factors found in tobacco smoke has several different, sometimes conflicting effects (42). Cigarette smoke promotes inflammation by inducing the production of various pro-inflammatory cytokines including IL-8 (43). IL-8 as a member of CXC chemokines represents a large family of chemotactic peptides with a wide range of cellular targets yield by stromal and epithelial cells of prostate and bladder. Leukocyte infiltration is the primary event in inflammation and the expression of chemokines temporally precedes that infiltration (44).

The present study reported that most BPH patients had a lower significant level of testosterone and higher non-significant level of creatinine, urea and uric acid as urinary tract disorder parameters. Vignozzi and colleagues also reported a typical prostate inflammatory phenotype and tissue remodeling accompanied by low serum testosterone (45), suggesting a key role of hypogonadism in the development of the BPH disease. Furthermore, numerous clinical studies have shown that patients with prostatitis have higher chances of developing BPH and low urinary tract symptoms, supporting the hypothesis that inflammation may lead to the development of BPH (46). Moreover, the inflammatory responses may stimulate the overproduction of ROS establishing testicular oxidative stress, which in turn may cause hormonal disturbance (47). Study results show a significant positive correlation between PSA and MDA levels and other inflammatory biomarkers. Data from other studies also showed a positive correlation between PSA and MDA levels. which considers MDA as an index of inflammation and oxidative stress in BPH patients (48). Inflammatory factor has been investigated in previous studies (49-54).

BPH smoking patients who had higher sera levels of PSA, IL-8 and MDA as an index of inflammation and oxidative stress might be at a higher risk of unfavorable pathophysiological outcomes of the disease.

Conflict of Interest

No conflict of interest.

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