WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 4, Issue 2, 118-138. Research Article ISSN 2277– 7105

THE POSSIBLE BENEFICIAL EFFECTS OF SELENIUM SUPPLEMENTATION IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA USING FINASTERIDE

Haidar Kadhim Al-Jawadi*[1], May S. Al-Sabbagh[2] and Yousuf M. Al-Hallaq[3]

[1]Specialist Clinical Pharmacist (Diploma), Clinical Pharmacy Section, Pharmacy Department, Ministry of Health, Iraq.

[2]Assist. Prof., Clinical Pharmacy Department, College of Pharmacy, University of Baghdad, Iraq.

[3]Consultant Urologist, FICMS FEBU, Urology Department, Alshaheed Ghazi Al-Hareeri Hospital for Specialized Surgeries, Baghdad, Iraq.

Article Received on
01 Dec 2014,

Revised on 26 Dec 2014,
Accepted on 21 Jan 2015

***Correspondence for Author**
Haidar Kadhim Al-Jawadi
Specialist Clinical Pharmacist (Diploma), Clinical Pharmacy Section, Pharmacy Department, Ministry of Health, Iraq.

ABSTRACT

Background: Aging in human males leads to imbalance between reactive oxygen species (ROS) formation and antioxidant capacity in favor of increasing the former which lead to benign prostatic hyperplasia (BPH). Selenium, a trace element, is found to possess antioxidant properties due to its involvement in the glutathione peroxidase enzyme. **Objective:** This study was implemented to evaluate the clinical and biochemical beneficial effects of selenium supplementation to improve the clinical and biochemical outcome parameters in a sample of Iraqi patients suffering from benign prostatic hyperplasia (BPH) using finasteride. **Methods:** Seventy individuals were enrolled in this study. Ten normal healthy individuals were set as a baseline. Twenty patients with BPH on finasteride 5mg daily were followed up for 3 months and considered as the control group. Forty other patients with BPH on finasteride 5mg daily were given selenium 200µg daily and followed up for the same 3 months. Biochemical and clinical parameters were reported monthly for the patient and control groups. They were serum prostate specific antigen (PSA), serum malondialdehyde (MDA), serum selenium level, international prostate specific score (I-PSS), and post-voidal residual volume (PVRV). **Results:** It was found that the group taking selenium showed a decrease in serum PSA and serum MDA and PVRV as

the selenium level was increased. The I-PSS score also showed a decrease as serum selenium level increased. **Conclusion:** Selenium has a beneficial effect on biochemical parameters in these patients attributed to its antioxidant properties; hence the clinical parameters also showed improvement.

KEYWORDS: selenium, antioxidant, benign prostatic hyperplasia

INTRODUCTION

The prostate is a gland surrounding the urethra and ejaculatory duct located inferior to the urinary bladder; it is composed of three glandular components – mucosal, submucosal and main glands; the latter being responsible for the secretory process, which depends on testosterone.[1] The gland is found to be essential for reproduction only, and not necessary for life. It weighs about 20g by age 20, and then starts to grow slowly after age 45. Benign prostatic hyperplasia (BPH) is a non-cancerous progressive condition affecting the majority of men as they are over the age of 50, due to an imbalance between cell proliferation and death. The compression on the urethra that it causes obstructs the flow of urine, giving rise to bladder and kidney infections, which are considered major complications of BPH. BPH is not a life threatening condition; however it affects the patient's quality of life (QoL). Clinical manifestations include lower urinary tract symptoms (LUTS), poor bladder emptying, urinary retention, detrusor instability, UTI, hematuria, and renal insufficiency.[2] Physical examination and digital rectal examination (DRE) and prostate specific antigen (PSA) assay are used for BPH diagnosis.

The International Prostate Symptom Score (I-PSS) is a validated short, self-administered questionnaire designed to be completed by the patient or general practitioners in urology clinics for diagnosis and follow-up of LUTS and impact on patient's quality of life (QoL). It has seven symptom questions: three dealing with storage symptoms (frequency, nocturia, urgency) and four with voiding symptoms (feeling of incomplete emptying, intermittency, straining, and a weak stream) + one question about the quality of life (QoL). The scoring ranges from 0-35: mild (0-8), moderate (8-19), and severe (20-35). A three-point improvement is a good sign. The scoring of the QoL question ranges from 0-6 (delighted to terrible).[3,4]

Alleviating bothersome LUTS resulting from prostate enlargement is the goal of treatment of BPH. Thus alteration of disease progression and prevention of complications are considered

in the guidelines.[5] Guidelines focus on health-related quality of life (HR-QoL) in making treatment decisions and assessments regarding BPH with LUTS to decrease psychological well-being.[6]

Finasteride is a 5-αRI which inhibits the type-2 isoform of 5α-reductase responsible for conversion of testosterone to dihydrotestosterone (DHT). It reduces size of the prostate by 20%, and reduces incidence of acute urinary retention and need for surgery.[7] It is widely distributed, but since its pharmacological effects are very specific to inhibition of 5α-reductase, and since only the prostate gland, the scalp, and the genital skin contain high concentrations of this enzyme, few adverse reactions will be seen in other organ systems.[8]

Oxidative stress (OS) reflects the imbalance between manifestations of ROS and ability of the defense mechanisms to detoxify the reactive intermediates or repair the resulting damage, and so shifting the oxidant/antioxidant balance towards oxidative stress. It is associated with either increased production of ROS or insufficient defense mechanisms, including superoxide dismutase (SOD), catalase (CAT), vitamins C, E, glutathione (GSH), trace elements (zinc, selenium, magnesium, cupper, etc), the resultant effect being a factor of the size of changes ranging from triggering apoptosis to cell death and necrosis.[9] Therefore antioxidative stress actions should include: avoiding sources of free radicals, increasing antioxidative capacity, and antioxidant intake.[10] Accumulating evidences suggest that aging-associated OS, resulting from oxidant-antioxidant imbalance (ROS production and defense mechanisms) is an important factor in prostate diseases, especially BPH. The deleterious effects of ROS on lipids, proteins and DNA on the prostate, and the effects of inflammation and hormonal deregulation contribute to the development of BPH and LUTS.[11,12] It has been found that activity of antioxidant enzymes is decreased in BPH in comparison to the normal prostate.[13] It is possible that BPH represents an alternate, non malignant pathway of unregulated prostate growth promoted by oxidative stress and inflammatory mediators.[14] The overall oxidative stress in humans cannot be precisely evaluated and applied to clinical practice by any of the known oxidative stress markers singly. The antioxidant enzyme expression in a certain tissue is the only approximation for it.[15] However, some oxidative stress markers are used to give a generalized picture of the oxidative stress.

Malondialdehyde (MDA) is a highly reactive dialdehyde generated by the degrading effect of ROS on polyunsaturated lipids by the process of lipid peroxidation (LP). LP is a mechanism by which cellular injury occurs, and its occurrence is an indicator of OS.[16] MDA is the most

abundant of LP products, and its presence has been shown to be related to the pathophysiology of different diseases, and its level is measured in plasma or serum and considered as a biomarker of OS and as an indicator of LP for these diseases and a tool for clinical management of patients.[17-19] It has been found that MDA levels increase in BPH patients, and so the involvement of OS in pathophysiology of BPH.[20]

Selenium (Se) is found naturally in the earth's crust. It occurs in different oxidation states: amorphous or polymeric elemental selenium (SeO), selenides (Se_2-), selenites (Se_4^+) and selenates (Se_6^+). Other forms are provided by food such as Se-amino acids, methylated forms, Se-proteins. Selenium is also released into the air through plant metabolism; it is also found in groundwater. However, the most important source of selenium for human beings is food; meats, sea-foods and cereals have the highest concentration of selenium in contrast to vegetables. FAO/WHO noted the wide range of dietary selenium intakes around the world. The extremities were 85-150µg/day in North America and 10-20µg/day in China.[21,22] Selenium rich foods are rarely consumed by people as meats and sea-foods are not affordable to the majority of people. Cereals are changeable sources of selenium according to their cultivation areas.[23-25] Studying diseases related to selenium deficiency have given rise to establishing recommended daily requirements for selenium in some countries. The reference daily intake (RDI) in UK is 60 - 75µg daily; in Australia 60-70µg daily; in the USA the recommended dietary allowances (RDA) is 55µg daily. The safe upper level (SUL) in UK is 450µg daily while the tolerable upper intake level in USA 400µg daily.[26-31] The WHO recommendation is 30-40µg selenium daily as a lower limit, and 400µg daily as a maximum daily safe intake.[32] Blood levels vary around the world owing to the variability of dietary selenium sources. It is 41.7µg/L in Finland, 60-80µg/L in New Zealand, 80.1µg/L in Poland, 158.2µg/L in Canada and 150-250µg/L in USA. [33-35]

Historically, selenium was discovered in 1817 by the Swedish chemist Berzelius, but its biological role was unknown until the work of Schwarz and Foltz in 1957. Years later, in 1973 it was found that its biochemical function was due to its involvement in glutathione peroxidase (GPx) enzymes,[36,37] which are considered as selenoproteins. They reduce lipid hydroperoxides to their corresponding alcohols, and catalyze breakdown of H_2O_2, then reducing it to water. By this it is considered the most powerful peroxide scavenger. [38,39]

Selenium is readily absorbed from the GIT. Its bioavailability is dependent on the form ingested. Selenite and selenate produce higher bioavailability as they are reduced to selenide

which is essential for selenocysteine, the active form of selenium in selenoproteins. Factors such as pregnancy, lactation, gut transit time, and gastrointestinal disorders affect bioavailability of selenium.[40,41] Absorption has been attributed to specific membrane transport proteins in the gastrointestinal tract. A variety of multiple membrane transport mechanisms take place for absorption.[42,23] The determination of selenium concentration and/or GPx in whole blood, plasma, serum, erythrocytes, platelets, urine, toenails and hair has been used to assess selenium status.[43]

Selenoproteins have been shown to play a role in slowing the aging process by slowing cellular damage,[44] thus selenium is required in adequate levels for the antioxidant systems for normal functioning.[45] The biochemical mechanism by which selenium exerts its defensive antioxidant effect is by incorporation in the form of selenocysteine in GPxs and thioredoxine reductase (TR).[46] It is considered to have two dose dependant modes of action; antioxidant through incorporation into selenoenzymes, and pro-oxidant by the direct effect of selenocompounds.[47] By these two modes of action it is involved in multiple steps of the antioxidant defense mechanisms mainly by radical scavenging and enzymatic decomposition of oxygen metabolites.[48] As there is a strong association between selenium, selenoenzymes and OS, so diseases associated with Se deficiency are shown to be related to LP in biological membranes, and may be due to elevated OS. [49,50] As a result any condition associated with increased oxidative stress or inflammation might be expected to be influenced by selenium levels.[40,51] The effect of selenium on non-tumorogenic BPH cells was found to be more than on malignant cells, as has been stated in the first report about selenium and BPH.[52] It has also been found that selenium maximized phytotherapeutic supplements' therapeutic effects in BPH. The proposed mechanisms where increasing apoptosis and retarding hormone dependent prostate growth.[53]

MATERIALS AND METHODS

This comparative randomized study was carried out at Alshaheed Ghazi Al-Hareeri hospital for specialized surgeries in Baghdad / Iraq. Recruitment of patients started from April 2014 till the end of September 2014. Clearance from the ethical committee in the college of pharmacy/ University of Baghdad, and from the Medical City in Baghdad was obtained before starting work. A follow-up sheet was designed for demographic, historical, and clinical data. Seventy individuals were enrolled in this study. Ten normal individuals were considered as baseline. Sixty patients with BPH were followed up for three months for

clinical observation and biochemical assessment. They were already diagnosed by the urologist to be confirmed cases of BPH and on finasteride (5mg daily). They were divided into two groups randomly. Group (A) were 40 patients who were given Selenium 200µg daily in addition to finasteride. Group (B) were 20 patients receiving finasteride only and were considered as controls. No interference was made to the usual dietary habits of the patients. In the first visit baseline socio-demographic data and clinical history were obtained from patients and controls. Current medications were also reviewed, including over-the-counter (OTC) and herbal medications. Blood samples were obtained by vein puncture, transferred to centrifuge tubes, then allowed to stand 2 hours at room temperature to clot, then centrifuged at 4000 rpm for 5 minutes to separate the serum. Serum samples were stored at -20ºC, until time of analysis. Follow-up of patients was on a monthly basis for three months. Any adverse event was also dealt with, whether serious or not. Education was given to the patient in the conversation about dealing with these events.

Inclusion Criteria

1. Symptoms from BPH for at least 6 months
2. Symptoms must meet the entrance criteria, as determined by a short questionnaire.
3. Enlargement of the prostate, as measured by the urologist.
4. At least 50 years of age, but not more than 90.

Exclusion Criteria

1- Prostate Cancer.
2- Blockage of major arteries in pelvis or other arterial abnormalities that prevent embolization or that might increase risks of injury by screening for these conditions.
3- Significantly decreased kidney function.
4- Prior prostate surgery, whether it has been performed via a scope or with conventional surgery.
5- Bladder or urinary conditions other than BPH requiring therapy.
6- History of cardiac rhythm abnormalities, congestive heart failure, uncontrolled diabetes, significant respiratory disease, or known immunosuppression.
7- History of clotting disorders.
8- Current medications (other than 5-alpha-reductase inhibitors), such as alpha-blockers, anti-cholinergics or antihistamines (in high therapeutic doses for long periods) within one month, and β-blockers, anticonvulsants within one week of treatment.

9- Active urinary tract infection.

10- Significant retained urine after voiding (>250ml) as measured by ultrasound.

11- Bladder stones or blood in urine within three months.

12- Previous rectal surgery, excluding hemorrhoidectomy, or history of rectal disease.

13- Prior pelvic irradiation or radical pelvic surgery.

Evaluation Sheet and I-PSS

The sheet in figure 1 was used for the monthly follow-up, in addition to the approved I-PSS sheet in figure 2 for the scoring procedure of prostatism.

Patient Follow-up Sheet				
Name				
Tel:				
Age: (>50years <90years)				
Occupation				
Date of first diagnosis of BPH: (symptoms for >6months)				
Prostate size:				
Hx of medications (including OTC):				
	Day 1 (first visit)	**After 1 month (second visit)**	**After 2 months (third visit)**	**After 3 months (fourth visit)**
Serum PSA				
Serum MDA				
serum selenium level				
U/S estimated Post-voidal Residual Volume (PVRV)				
I-PSS Urinary Symptom				

Figure 1: Patient Follow-up Sheet

In the past month	**Not at All**	**< than 1 in 5 Times**	**< than Half the Times**	**About Half The Times**	**> than Half the Time**	**Almost Always**
1-Incomplete Emptying: How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5
2-Frequency: How often have you had to urinate less than every 2 hours?	0	1	2	3	4	5
3-Intermittency: How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4-Urgency: How often have you found it difficult to postpone urination?	0	1	2	3	4	5
5-Weak Stream: How often have you had a weak urinary stream?	0	1	2	3	4	5

6-Straining: How often have you had to strain to start urination?	0	1	2	3	4	5
	None	1 time	2 times	3 times	4 times	5 times
7-Nocturia: How many times did you typically get up at night to urinate?	0	1	2	3	4	5
Total IPSS score						

Score: 0-7: Mild 8-19: Moderate 20-35: Severe

Quality of Life Due to Urinary Symptoms	**Delighted**	**Pleased**	**Mostly Satisfied**	**Mixed**	**Mostly Dissatisfied**	**Unhappy**	**Terrible**
If you were to spend rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Figure 2: I-PSS sheet

Lab and diagnostic Analysis

Serum PSA levels were determined with the commercial Kit (ELISA Test for the Quantitative Determination of Prostate Specific Antigen in Human Serum) available from (Human Gesellschaft für Biochemica und Diagnostica mbH. Germany). Serum MDA levels were determined with a commercial Kit (CUSABIO BIOTECH CO., LTD) using the ELISA technique. Serum selenium concentration was determined using the hydride generation atomic absorption spectrometry ; 500 µL of serum sample were diluted 1+2 with 0.1% V/V nitric acid and 0.1% Triton X-100, and 10 µL were introduced into graphite furnace with appropriate volume of palladium modifier and iridium modifier. The PVRV was measured by the ultrasonography which is considered as a reliable method for this assessment.

Statistics

Statistical Package for Social Sciences (SPSS), version 17, was used for data analysis. Results were expressed as mean ±standard deviation. Tests of statistical significance were carried out using one-way analysis of variance (ANOVA) wherever more than two groups were analyzed. T-test analysis was carried out wherever two groups were to be studied.

RESULTS

Age distribution

Individuals enrolled in the study were 70 males. Their distribution in the study is shown in table 1. The ages were consistent with the inclusion criteria of the study.

Table 1: Distribution of individuals in the study

Group	Number of patients (n)	Age
Group A	40	62.48 ± 7.14
Group B	20	60.95 ± 6
Baseline	10	62.2 ± 6.47

Differences in parameters between normal individuals and BPH patients in this study.

The first analytical procedure was to compare between the patients and the healthy individuals in general regardless of the effect of adding selenium to the finasteride regimen of the BPH patients. This is shown in table 2 expressed as mean ± STD, as well as the significance.

Table 2: The clinical and biochemical parameters at the start of the study

Parameters (mean ± STD)	Group A (n=40)	Group B (n=20)	Baseline (n=10)	Significance (as p value)
Serum PSA (ng/mL)	3.723 ± 2.912	3.995 ± 2.203	1.301 ± 0.768	0.017
Serum MDA (µmol/L)	3.421 ± 1.67	3.342 ± 1.533	2.046 ± 0.77	0.043
Serum Selenium (µg/L)	56.4775 ± 4.95	51.855 ± 2.12	53.85 ± 1.82	0.912

The Effect of Adding Selenium to Finasteride on Different Clinical and Biochemical Parameters in BPH Patients

Table 3: The clinical and biochemical parameters along the study period

Parameters (mean ± STD)	Visits	Group A (n=40)	Group B (n=20)	Baseline (n=10)
Serum PSA (ng/mL)	1st	3.723±2.912[c,a]	3.995±2.203[c]	1.301±0.768
	2nd	3.516±2.385	3.919±2.420	
	3rd	3.249±2.093	3.938±2.353	
	4th	2.957±1.759[d]	4.075±2.133	
Serum MDA (µmol/L)	1st	3.421±1.67[e,b]	3.342±1.533[b]	2.046±0.77
	2nd	3.084±1.262	3.722±1.134	
	3rd	2.800±1.312	3.376±1.27	
	4th	2.424±1.072[d]	3.386±1.395	
PVRV (mL)	1st	26.03±16.146[e,a]	32.95±16.972[b]	
	2nd	23.23±16.14	34.45±17.304	
	3rd	20.65±14.67	30.2±12.846	
	4th	15.6±13.22[f]	29±8.22	
I-PSS	1st	20.4±5.532[e,a]	21.05±6.533[b]	
	2nd	18.25±4.813	21.15±6.055	
	3rd	15.75±5.108	20±3.839	

	4th	13.33±5.101[d]	20.5±4.947	
QoL score	1st	3.5±0.877[e,b]	3.55±0.945[c]	
	2nd	2.63±0.774	3.2±0.894	
	3rd	2.15±0.533	3.25±0.851	
	4th	1.75±0.63[d]	3.05±0.605	

Continuous variables presented as mean ± STD;

[a] results compared with other group non-significant ($p<0.05$)

[b] results compared within same group non-significant ($p<0.05$)

[C] results within the same group significant at $p<0.05$.

[d] results compared with other group highly significant at $p<0.01$.

[e] results within the same group very highly significant at $p<0.001$.

[f] results compared with other group very highly significant at $p<0.001$.

Serum PSA: In the 1st visit the difference between the three groups was significant ($p<0.05$). However, the difference between group A and group B didn't show significance ($p>0.05$). The difference between the results of the 1st and 4th visit for group A and group B were significant ($p<0.05$). However, the difference between group A and group B at the 4th visit was highly significant at $p<0.01$. It was also seen that there was no significance of difference between the 1st and 3rd visit in group A ($p >0.05$), and that the significance of difference started in the 4th visit.

Serum MDA: It is shown that there is significance ($p<0.05$) between the three groups at the 1st visit. There was a very highly significant difference ($p<0.001$) between the results of the 1st visit and 4th visit for group A. The difference in results between group A and group B in the 1st visit was non-significant ($P >0.05$). There was a significant difference between the results of 1st visit and 4th visit in group B ($p< 0.05$). However, the results of the 4th visit between group A and group B were very highly significant ($p <0.001$). Moreover, the difference between the result of the 1st visit and the 2nd visit for group A was non-significant ($p >0.05$).

PVRV: The difference in the 1st visit and 2nd visit for group A was significant ($p<0.05$). The differences between the 1st visit and the 3rd and 4th visits were very highly significant ($p<0.001$). In comparing the difference between the 1st visit and the 4th visit for group B, the difference was not considered significant ($p>0.05$). The comparison between group A and B showed that the difference at the 1st visit was non-significant ($p >0.05$), while the difference between results at the 4th visit was very highly significant ($p<0.001$).

I-PSS scores: The difference of results between the 1st visit and the 4th visit in group A was very highly significant ($p<0.001$). The difference between the results of the 1st visit and the 2nd visit started to show high significance ($p<0.01$). The difference between the results between the 1st visit and the 4th visit in group B showed non-significance ($p>0.05$). The difference of results between group A and B, were non-significant ($p>0.05$) at the 1st visit and highly significant ($p<0.01$) at the 4th visit.

QoL Score: The difference between the results for group A were very highly significant ($p<0.001$) between the 1st visit and 2nd 3rd and 4th visits. The difference between the results for group B between the 1st visit and 2nd and 3rd visits were non-significant ($p>0.05$), while the difference between the 1st visit and the 4th visit was significant ($p<0.05$). The comparison between group A and B showed non-significance between the results at the 1st visit ($p >0.05$), while at the 4th visit the p-value showed high significance ($p <0.01$).

DISCUSSION

This study was designed and applied as a comparative study, to evaluate the effects of adding selenium to finasteride in BPH patients. It is not allowed from the ethical point of view to use selenium alone for treatment of BPH, as it is not yet approved in the guidelines for treatment.[3] Selenium tablets taken orally were generally well tolerated. No significant adverse effects were documented in the patients who received them. Other studies[54] have shown that selenium with silymarin given orally to BPH patients were devoid of significant adverse effects.

The Selenium Level: As soon as this study was prepared, no data regarding the blood selenium levels in Iraqi population was available. In our study, the mean and standard deviation of serum selenium level in a sample of healthy individuals with the age of 62.2±6.47 years was 53.85±1.82 µg/L, Data from an Iranian study showed serum selenium levels of 100.6 ± 12.8 µg/l, which was stated to be similar to the level reported in a survey in Saudi Arabia.[55] Other studies in a variety of geographical areas around the world showed data such as 67.4±11.7ng/ml in Poland,[56] 145±47ng/ml in Rajasthan (India),[57] 129±21.5µg/L in Taiwan,[58] 78.2±7.5µg/L in Sudan,[59] and 91.71±18.7µg/L in Egypt.[60] The normal values which are set as reference ranges differ from country to another such as 80–120µg/L[61] in Europe or 80-250µg/L in USA.[62] From these data we conclude that our patients have low levels of serum selenium. Our study also revealed that the serum selenium

in the two BPH patients groups showed non-significant ($p>0.05$) difference at the 1st visit. These results are consistent with other studies regarding BPH patients. Monika et al found that the increase in serum selenium concentration significantly decreased the risk of BPH.[63] Minutoli et al also found that prostate overweight and growth was significantly suppressed by administration of selenium.[53] Zachara B. et al have also shown that plasma selenium levels were lower in BPH patients than normal subjects.[64] The difference between the three groups enrolled in our study was not significant ($p>0.05$) which can indicate that the selenium level in the population may not be a direct cause of BPH in males. Similar results have been shown in other studies; Muecke R. et al have shown that the difference in whole blood level of selenium between healthy and BPH patients was not significant ($p=0.13$).[65] The level of serum selenium during the three months of our study showed increments that were non-significant in the 1st month ($p>0.05$), but then started to show significance in the 2nd month ($p<0.01$), and reached a very highly significant level in the 3rd month ($p<0.001$). The difference in the serum selenium level between the patients who received selenium and those who didn't receive it was also very highly significant ($p<0.001$). Our results have the opportunity of getting beneficial clinical outcomes in a short time with a rapid onset of action.

The Effect of Selenium on PSA: The analysis of the results we got in our study revealed that there was change in serum PSA levels between and within the groups. At the beginning of the study the serum PSA levels between the patient and control groups and the normal healthy individuals' group showed significant difference. The mean serum PSA in the healthy individuals was 1.3±0.76ng/mL, whereas the mean in the patient and control groups (which were both suffering from BPH) were 3.723±2.9ng/mL and 3.995±2.2ng/mL respectively. This means that the serum PSA in the latter two groups was at the upper normal limit which is 4ng/mL. These results are consistent with the study of Savas M. et al which showed that PSA levels were significantly higher in BPH patients than in controls ($P=0.001$). [66] In the study of Estrada-Carrasco CE. et al the PSA level in patients with BPH was 5.8ng/mL, [67] while in the study of Duru R. et al. it was 8.1±9ng/mL. [68] The change in the serum PSA in our study showed significant difference ($P<0.05$) after the three months treatment period with selenium. These results are consistent with the study of Vostalova et al who used selenium with silymarin for treatment of patients with BPH with the exception that we used selenium alone without silymarin.[54] El-Bayoumy K. et al showed in their study which lasted 9 months, that selenium significantly decreased PSA levels after 3 months of

supplementation.[69] Our study also showed that the serum PSA level witnessed non-significant decrease in the first two months of treatment, but started to be significant in the third month. From these results we conclude that it is essential for selenium treatment to be continuous or its effect on PSA will vanish.

The Effect of Selenium on MDA: Serum MDA was the most important biomarker used in our study to evaluate the effect of selenium on the oxidative stress condition in BPH patients. It was valuable to compare the baseline results with other studies to have a clinical picture about the oxidative stress condition in our patients. MDA levels at the beginning of our study showed significant differences ($p<0.05$) between the three groups. The serum MDA levels were 2.046±0.77, 3.421±1.67, 3.342±1.533µmol/L for healthy individuals, patients and control groups respectively. At the end of the first month of selenium administration the difference of MDA was not-significant ($p>0.05$); while after three months there was a very highly significant difference ($p<0.001$). It has been stated that the formation of the seleno-enzymes, mainly glutathione peroxidase (GPx) was enhanced upon administration of selenium. This enzyme plays an important role in protecting cells against oxidative damage by scavenging free radicals. The increments in GPx levels and hence the decrease in the oxidative stress were highly correlated with increasing selenium levels. This supports the hypothesis that selenium is involved in the mechanisms of reducing OS.[69] The difference in serum MDA levels between the healthy individuals and the BPH patients in our study strengthens the fact that high OS may be one of the factors responsible for BPH development. In the light of the strong positive correlation found between PSA and MDA levels in our study, we can speculate that increased MDA levels might be considered a useful marker of LP of prostate epithelium.[20] The high MDA levels in both patient and control groups (which are both suffering from BPH) is an indicator of high LP. On the other hand, the relatively low selenium level is correlated with low antioxidant activity. Free radicals produced in the process of LP may be destructive to the prostate tissue, if not scavenged by the antioxidant enzymes, and hence BPH ensues. In spite of the scanty studies that show the increased MDA levels in BPH our study elucidated that the lowering of serum MDA and PSA levels with the increase of selenium levels indicate that OS is implicated in the etiology of BPH. Our study has also shown that there is a direct relationship between serum MDA and PSA levels, and an inverse relationship between them and serum selenium levels. This is consistent with the studies of Akinloye et al who also described the inverse relationship between antioxidant levels and serum PSA in BPH patients.[68,70] Studies that have shown the inverse relationship

between serum GPx levels and BPH,[70] and the direct relationship between serum MDA levels and BPH, [71] can be used to explain the results we reached in our study. Selenium is a component of the GPx enzyme, which is responsible for the detoxification of H_2O_2. As selenium level is lowered, GPx decreases leaving the high levels of .OH radicals to result in prostate tissue destruction. The high serum MDA levels in BPH is an indicator of enhanced OS, which could be either due to overproduction of free radicals resulting in depletion of antioxidant enzymes, or due to low levels of these enzymes due to deficiency in their components.

The Effect of Selenium on PVRV: The PVRV is the volume of urine that remains in the bladder after micturition. The normal value is considered to be 0.09 – 2.24mL.[2] It is considered to be one of the clinical parameters for evaluation of treatment regimens. The results from our study showed very highly significant differences ($p<0.001$) in PVRV after three months of treatment within the patient group and between the patient and control groups. The changes were from 26.03±16.146mL down to 15.6±13.22mL in three months. Vostalova J. et al showed results where the differences between treatment and control groups were significant ($p<0.05$).[54] The difference could be due to the high selenium levels achieved in our study. However, as the PVRV is a function of two components of BPH; the static component represented by enlargement of the prostate leading to bladder outlet obstruction (BOO), and the dynamic component represented by the poor detrusor muscle functioning, therefore it is considered of little sensitivity for detecting true positive cases of obstruction.[3]

The Effect of Selenium on I-PSS and QoL Scores: In our study these scores were used to evaluate the clinical outcome of the treatment in the patient and control groups. At the starting point of the study, there was non-significant difference ($p>0.05$) between the two groups (A and B) in both I-PSS and QoL scores; however, after three months there was a very highly significant difference ($p<0.001$) between them. These results were consistent with the statistically significant results ($p<0.05$) of Vostalova J. et al. [54] Our study also showed that there was a one-point improvement in the control group (who used finasteride alone) according to the I-PSS scores which was lower than the 3 points pointed by AUA.[4] The difference could be due to the short period of our study which was only three months of patient follow-up. It has also been shown in our study that there was a 7 point improvement in the patient group (who used selenium in addition to finasteride). This could strengthen the

hypothesis of OS effect on the etiology of BPH. The QoL score was highly affected by the selenium supplementation with a very highly significant difference ($p<0.001$) in the patient group, and a highly significant difference ($p<0.01$) between the patient and control groups after 3 months of treatment. It has also been shown in other studies that this score is the most affected score (42.3% of patients) although about half of the BPH patients stay having unsatisfactory outcomes in spite of their treatment.[72]

CONCLUSION AND RECOMMENDATIONS

1- This study showed that supplementation of selenium as an antioxidant shifted the oxidant-antioxidant balance in favor of the antioxidant side. It also showed that increasing antioxidant levels had a beneficial effect in lowering biochemical and clinical markers of BPH and improvement of signs and symptoms at well tolerated doses.

2- Lifestyle-related habits should be improved before starting supplements to increase the own anti-oxidative capacity of the patient.

3- Further work regarding the cost-effectiveness of using selenium in treatment courses of BPH may be proposed.

REFERENCES

1. Junqueira LC., and Carneiro J., Basic Histology, 4th edition, Lange Medical Publications & Libraire du Liban, 1983; 465.
2. Lepor H., Evaluating men with benign prostatic hyperplasia, Reviews in Urology, 2004; 6(suppl 1), s8-s15.
3. The management of lower urinary tract symptoms in men, Published by the National Clinical Guideline Centre at The Royal College of Physicians, London, NW11 4LE , First published 2010.
4. American Urological Association Guideline: Management of Benign Prostatic Hyperplasia (BPH)Revised, 2010, American Urological Association Education and Research, Inc®.
5. Roehrborn C, Burkhard F, Bruskewitz R et al: The effects of transurethral needle ablation and resection of the prostate on pressure flow urodynamic parameters: analysis of the United States randomized study. J Urol, 1999; 162: 92.
6. Desgrandchamps F, de la Taille A, Azzouzi A, Fourmarier M, Haillot O, Lukacs B et al, Management of non-complicated BPH: proposition of a renewed decision tree. World J Urol., 2006, 24(4): 367–370.

7. Wasson JH. Finasteride to prevent morbidity from benign prostatic hyperplasia. N Eng J Med, 1998; 338: 612-13.
8. Steiner JF. Clinical pharmacokinetics and pharmacodynamics of finasteride. Clin Pharmacokinet, 1996; 30: 16-27.
9. Lennon SV, Martin SJ, Cotter TG, "Dose-dependent induction of apoptosis in human tumour cell lines by widely diverging stimuli". Cell Prolif., 1991; 24(2): 203–14.
10. Yuji Naito, Masaichi-Chang-il Lee, Yoji Kato, Ryoji Nagai, Yoshikazu Yonei, Oxidative Stress Markers, Anti-Aging Medicine, 2010; 7(5): 36-44.
11. Srivastava D.S.L. and Mittal R.D., Free radical injury and antioxidant status in patients with benign prostate hyperplasia and prostate cancer, Indian Journal of Clinical Biochemistry, 2005, 20(2): 162-165.
12. Bostanci Y., Kazzazi A., Momtahen S., Laze J. and Djavan B., Correlation between benign prostatic hyperplasia and inflammation, Curr Opin Urol, 2013; 23: 5-10.
13. Aydin A, Arsofa-Sarafinovska Z, Sayal A, Eken A, Erdem O, Erten K, Ozgok Y, Dimovski A. Oxidative stress and antioxidant in non-metastatatic prostate cancer and benign prostatic hyperplasia. Clin Biochem, 2006; 39: 176–9.
14. Malins DC, Johnson PM, Barker EA, Polissar NL, Wheeler TM, Anderson KM. Cancer-related changes in prostate DNA as men age and early identification of metastasis in primary prostate tumors. Proc Natl Acad Sci USA., 2003; 100: 5401–6.
15. Ripple O, William F, Randall P,Wilding G. Prooxidant–antioxidant shift induced by androgen treatment of human prostate carcinoma cells. J Natl Cancer Inst, 1997; 89(1): 40-48.
16. Janero DR., Malondialdehyde and thiobarbituric acid-reactivity as diagnostic indices of lipid peroxidation and peroxidative tissue injury. Free Radic Biol Med. 1990; 9:515-540.
17. Moore K., Roberts LJ., Measurement of lipid peroxidation. Free Radic. Res, 1998; 28(6): 659–71.
18. Del Rio D, Stewart AJ, Pellegrini N.A., Review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. Nutr Metab Cardiovasc Dis, 2005; 15: 316-28.
19. Meagher EA, Fitz Gerald GA. Indices of lipid peroxidation in vivo: strengths and limitation. Free Radic Biol Med, 2000; 28: 1745-1750.
20. Merendino RA, Salvo F, Saija A, Pasquale GD, Tomaino A, Minciullo PL, Fraccica G, and Gangemi S, Malondialdehyde in benign prostate hypertrophy: a useful marker? Mediators of Inflammation, April 2003; 12(2): 127-128.

21. Pedrero Z., Madrid Y., Novel approaches for selenium speciation in foodstuffs and biological specimens: A review. Analytica chimica acta, 2009; 634(2): 135-152.
22. WHO/HSE/WSH/10.01/14, Selenium in Drinking-water, Background document for development of WHO Guidelines for Drinking-water Quality, 2011.
23. Susan J. Fairweather-Tait, Yong ping Bao, Broadley MR., Collings R., Ford D., Hesketh JE., and Hurst R., Selenium in Human Health and Disease, Antioxidants & redox signaling, 2011; (14): 7.
24. Rayman MP, Infante HG, and Sargent M. Food-chain selenium and human health: spotlight on speciation. Br J Nutr, 2008; 100: 238–253.
25. Wolf WR. and Goldschmidt RJ. Updated estimates of the selenomethionine content of NIST wheat reference materials by GC-IDMS. Anal Bioanal Chem, 2007; 387: 2449–2452.
26. Tinggi U, Selenium: its role as antioxidant in human health, Environ Health Prev Med, 2008; 13: 102–108.
27. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington DC: National Academy Press, 2000.
28. Department of Health and Ageing. Nutrient Reference Values for Australia and New Zealand. Canberra: Commonwealth of Australia, 2006.
29. Expert Group on Vitamins and Minerals. Safe Upper Levels for vitamins and minerals (May 2003). Available at: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf.
30. Food and Nutrition Board, Institute of Medicine (U. S.). Dietary reference intakes for vitamin C, vitamin E, selenium and carotenoids. National academies press, 2000; 506.
31. Tinggi U. Selenium toxicity, its adverse health effects. In: Preed V., Watson R. editors. Reviews in food and nutrition toxicity. Boca Raton: CRC Press, 2005; 29–55.
32. World Health Organization. Selenium. In: Trace elements in human nutrition and health. Geneva: WHO, 1996; 105–22.
33. Lockitch G: Selenium: clinical significance and analytical concepts. Crit Rev Clin Lab Sci, 1989; 27: 483-541.
34. Wasowicz W, Zachara BA, Selenium concentrations in the blood and urine of a healthy Polish sub-population, J Clin Chem Clin Biochem, 1987; 25: 409-412.
35. Xia Y, Hill KE, Burk RF, Biochemical studies of a selenium-deficient population in China: measurement of selenium, glutathione peroxidase and other oxidant defense indices in blood, The journal of nutrition, 1989; 1318-1326

36. Schwarz K, Foltz CM. Selenium as an integral part of factor 3 against dietary necrotic liver degeneration. J Am Chem Soc., 1957; 79: 3292.
37. Rotruck JT, Pope AL, Ganther HE, Swanson AB, Hafeman DG, Hoekstra WG. "Selenium: biochemical role as a component of glutathione peroxidase". Science 1973; 179: 588.
38. Muller F. L., Song W., Liu Y. et al., Absence of Cu Zn superoxide dismutase leads to elevated oxidative stress and acceleration of age-dependent skeletal muscle atrophy, Free Radical Biology and Medicine, 2006; 40(11): 1993–2004.
39. Brown KM, Arthur JR. "Selenium, selenoproteins and human health: a review". Public Health Nutr, 2001; 4: 593.
40. Rayman MP, "The importance of selenium to human health", The Lancet, July 2000; 15: 356.
41. Jackson MJ. "The assessment of bioavailability of micronutrients: introduction". Eur J Clin Nutr, 1997; 51: S1.
42. Nickel A, Kottra G, Schmidt G, Danier J, Hofmann T, and Daniel H. Characteristics of transport of selenoaminoacids by epithelial amino acid transporters. Chem Biol Interact, 2009; 177: 234–41.
43. NÈVE J. Biological parameters for assessing selenium status. In: Selenium in Medicine and Biology, Nève J., Favier A., eds., Walter de Gruyter & Co., Berlin-New York, 1989; 137-147.
44. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature, 2000; 408: 239–47.
45. Foster, L. H., Selenium in the environment, food, and health. Nutrition and Food Science, 1995; 95: 17–23.
46. Flohe L, Gunzler WA, Schock HH, Glutathione Peroxidase: A Selenoenzyme, FEBS letters, 1973; 32(1): 132-134.
47. Mugesh G., & Singh HB., Synthetic organoselenium compounds as antioxidants: Glutathione peroxidase activity. Chemical Society Reviews, 2000; 29: 347–357.
48. Brenneisen P, Steinbrenner H, Sies H., Selenium, oxidative stress, health aspects. Mol Aspects Med, 2005; 26: 256–67.
49. Tapiero H., Townsend DM., Tew KD., The antioxidant role of selenium and seleno-compounds, Biomedicine & Pharmacotherapy, 2003; 57: 134–144.
50. Moghadaszadeh B, Beggs AH. Selenoproteins and their impact on human health through diverse physiological pathways. Physiology, 2006; 21: 307–315.

51. Underwood EJ, in: Trace elements in human and animal nutrition (Academic Press Ind., New York and London, 1962; 291-324.
52. NurÖzten Kandaş, Randolph C., Bosland MC., Differential Effects of Selenium on Benign and Malignant Prostate Epithelial Cells: Stimulation of LNCaP Cell Growth by Noncytotoxic, Low Selenite Concentrations, Nutr Cancer, 2009; 61(2): 251.
53. Minutoli L., Altavilla D., Marini H., Rinaldi M., Irrera N., Pizzino G., Bitto A., Arena S., Cimino S., Squadrito F., Russo GI., Morgia G., Inhibitors of apoptosis proteins in experimental benign prostatic hyperplasia: effects of serenoarepens, selenium and lycopene, Journal of Biomedical Science, 2014; 21: 19.
54. Vostalova J., Vidlar A., Ulrichova J., Vrbkova J., Simanek V., Student V., Use of selenium-silymarin mix reduces lower urinary tract symptoms and prostate specific antigen in men, Phytomedicine, Dec 2013; 21(1): 75-81.
55. Safaralizadeh R., Kardar GA., Pourpak Z., Moin M., Zare A., and Teimourian S.; Serum concentration of Selenium in healthy individuals living in Tehran; Nutrition Journal, 2005; 4: 32.
56. Czuczejko J., Zachara BA., Topczewska ES., Halota W., and Kędziora J., Selenium, glutathione and glutathione peroxidases in blood of patients with chronic liver diseases, Acta Biochimica Polonica, 2003; 50(4): 1147–1154.
57. Goyal MM., Kalwar AK., Vyas RK. And Bhati A.; A study of serum zinc, selenium and copper levels in carcinoma of esophagus patients; Indian Journal of Clinical Biochemistry, 2006; 21(1): 208-210.
58. Lin CC., Hiang JF., Tsai LY., Huang YL., Selenium, Iron, Copper, and Zinc levels and Copper-to-Zinc ratios in serum of patients at different stages of viral hepatic diseases, Biological trace element research, 2006; 109: 15-23.
59. Hussein MM., Yousif AA., Saeed AM., Serum Levels of Selenium, Zinc, Copper and Magnesium in Asthmatic Patients: a Case Control Study, Sudan JMS Mar, 2008; 3(1).
60. El-Sherbeny SSA., Abd Allah AM., Massoud W., Copper, Zinc, Selenium, Cadmium and Lead Levels in plasma of Hemodialysis Patients, The Egyptian Journal of Hospital Medicine, 2006; 24: 556 – 563.
61. Skesters A., Rozentale B., Voicehovska J., Zvagule T., Rainsford KD., Silova A., Rusakova N., Petuhovs V., Ivanchenko L., Larmane L., Fluorescence Method for Selenium Determination in the Blood Plasma of Bronchial Asthma, Hepatitis C Virus, HCV/HIV Co-Infection Diseases and Post-Chernobyl Syndrome Patients, Polish J. of Environ. Stud, 2006; 15(4A): 94-96.

62. Thomsonc D., Assessment of requirements for selenium and adequacy of selenium status: a review. Eur. J. Clin. Nutr, 2004; 58: 391.
63. Monika E., Astrid S., Rudolf K., Birgit T., Jakob L., Sabine R., Effects of selenium status, dietary glucosinolate intake and serum glutathione S-transferase α activity on the risk of benign prostatic hyperplasia, BJU International, Dec 2012; 110(11c): E879-E885.
64. Zachara BA., Szewczyk-Golec K., Tyloch J., Wolski Z., Szylberg T., Stepien S., Kwiatkowski S., Bloch-Boguslawska E., Wasowicz W.; Blood and tissue selenium concentrations and glutathione peroxidase activities in patients with prostate cancer and benign prostate hyperplasia; Neoplasma, 2005; 52(3): 248-54.
65. Muecke R., Klotz T., Giedl J., Buentzel J., Kundt G., Kisters K., Prott FJ., Micke O., Whole blood selenium levels (WBSL) in patients with prostate cancer (PC), benign prostatic hyperplasia (BPH) and healthy male inhabitants (HMI) and prostatic tissue selenium levels (PTSL) in patients with PC and BPH, Acta Oncologica, 2009; 48: 452-456.
66. Savas M., Verit A., Ciftci H., Yeni E., Aktan E., Topal U., Erel 0., Oxidative Stress in BPH, J Nepal Med Assoc, 2009; 48(173): 41-5.
67. Estrada-Carrasco CE., Flores-Terrazas JE., Floriano-Sánchez E., Castro-Marín M., López-Silvestre JL., Campos-Salcedo JG., Zapata-Villalba MA., Mendoza-Álvarez LA., Cárdenas-Rodríguez N., Regulation of antioxidant enzymes as prostate tumor markers, Rev Mex Urol, 2010; 70(3): 157-163.
68. Duru R., Njoku O., and Maduka I., Oxidative Stress Indicators in Patients with Prostate Disorders in Enugu, South-East Nigeria, Bio Med Research International Volume 2014, Article ID 313015, 6 pages.
69. El-Bayoumy K., Richie JP., Boyiri T., Komninou D., Prokopczyk B., Trushin N., Kleinman W., Cox J., Pittman B., and Colosimo S., Influence of selenium-enriched yeast supplementation on biomarkers of oxidative damage and hormone status in healthy adult males: a clinical pilot study, Cancer Epidemiology, Biomarkers & Prevention, Nov 2002; 11: 1459–1465.
70. Akinloye O., Adaramoye O., and Kareem O., Changes in antioxidant status and lipid peroxidation in Nigerian patients with prostate carcinoma, Polskie Archiwum Medycyny Wewnetrznej, 2009; 119(9): 526–532.
71. Ahmad M., Suhail N., Mansoor T., Banu N., Ahmad S., Evaluation of Oxidative Stress and DNA Damage in Benign Prostatic Hyperplasia Patients and Comparison with Controls, Ind J Clin Biochem, (Oct-Dec 2012); 27(4): 385–388.

72. Fourcade RO., Lacoin F., Roupreˆt M., Slama A., Le Fur C., Michel E., Sitbon A., EmeryCotte´ F., Outcomes and general health-related quality of life among patients medically treated in general daily practice for lower urinary tract symptoms due to benign prostatic hyperplasia, World J Urol, 2012; 30: 419–426.