Oxidative Stress in Patients with Benign Prostate Hyperplasia

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ABSTRACT

Benign Prostate Hyperplasia (BPH) is a common health problem in aging male. Free radicals and Reactive Oxygen Species (ROS) are produced in overwhelming quantity with advancement of age. When in oxidative stress, these reactive species cause extensive damage to various organ in the body, may be associated with pathogenesis of BPH also. This study aimed at assessing Malondialdehyde (MDA), the marker of lipid peroxidation and anti-oxidants e.g. α-Tocopherol and Ascorbate status in plasma in BPH patients. Forty eight (n=48) cases of BPH and forty six (n = 46) healthy age matched controls were enrolled. Plasma MDA level showed 4.81±1.87 nmol/ml in cases compared to 3.69±1.56 nmol/ml in healthy controls ($p< 0.001$). There were significant decrease in plasma α-Tocopherol and ascorbate level which were 0.85±0.12 mg/dl and 0.93 ± 0.13 mg/dl in cases compared to 1.37±0.31 mg/dl and 1.44±0.38 mg/dl in healthy controls respectively. Inverse correlation of plasma MDA with α-Tocopherol ($r = -0.09$, $p>0.05$) and Ascorbate ($r =-0.51$, $p=0.008$) was found in BPH patients. There was mild elevation of PSA in BPH patients compared with control but was not statistically significant. Thus, our study showed the evidence of association of oxidative stress in BPH patients.

Key words: *Benign Prostate Hyperplasia, Malondialdenyde, Oxidative Stress*

INTRODUCTION

Benign Prostate Hyperplasia (BPH), a common disease affecting the aging male, is an endocrine disorder, requires the action of testicular androgen and growth factors on their receptors in prostate gland for its pathogenesis. The prostatic level of dihydrotestosterone (DHT) as well as androgen receptor remains high with ageing causing increased proliferation of prostate despite the fact that peripheral level of testosterone decreases.[1] BPH occurs in the transitional zone which involves the four major cell types in the prostate smooth muscle cell, fibroblast, acinar and basal epithelium.[2]

Oxidative stress is imbalance of antioxidants & pro-oxidants in favor of pro-oxidants. Antioxidants are substances that are capable of competing with the other oxidizable substrate and thus significantly delay or inhibit the oxidation of these substrates. To prevent the series of reaction leads to free radical generation as Reactive Oxygen Species (ROS) and to scavenge

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these ROS, scavenging system is present in the body which protects the body from these devastating free radicals. Enzymatic antioxidants such as Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx) and Catalase (CAT) as well as vitaminic antioxidants namely, α-tocopherol and ascorbate play a major role as a scavenger of free radicals.

Malondialdehyde is a physiological keto-aldehyde produced as a by-product of peroxidative decomposition of unsaturated lipid like arachidonic acid. MDA is also a secondary product of lipid peroxidation and is used as an indicator of free radical tissue damage.[3] Increasing evidence has indicated that oxidative stress is associated with aging and several age related degenerative diseases including cancer.[4] A wide variety of reactive oxygen species (ROS) and reactive nitrogen species (RNS) attack DNA directly and form mutagenic lesion. ROS may cause formation of adducts indirectly by inhibiting autocatalytic lipid peroxidation which generates a large variety of genotoxic breakdown products including alkoxyl radicals, peroxyl radicals and aldehyde such as malondialdehyde.[5]

Therefore, the estimation of Malondialdehyde, vitaminic antioxidants i.e. α-Tocopherol and ascorbate level provides the extent of oxidative stress in patients with BPH.

MATERIALS AND METHODS

This hospital based case control study was carried out in B. P. Koirala Institute of Health Sciences, Dharan, in which 48 male patients with BPH and 46 healthy age matched males as a control were enrolled after taking informed consent from all the participants. Patients with signs and symptoms of BPH, positive digital rectal examination and confirmed by histological examination on biopsy samples were included in the study. However patients with liver dysfunction, diabetes mellitus, smokers and other infections were excluded from the study. Blood was collected in EDTA vials and centrifuged at 2000 rpm for 15 minutes for separation of plasma. MDA was estimated by method based on the formation of red pigment condensation of lipid peroxidation breakdown products like MDA with thiobarbituric acid.[6] α-Tocopherol was estimated by the method in which α-Tocopherol is oxidized to tocopheryl quinine by ferric chloride and resultant ferrous ion is complex with ethanolic α, α' – Dipyridyl to produce a red colored compound.[7] Plasma Ascorbate was estimated by method depending on the reduction of ferric ion to ferrous ion by ascorbic acid, forming a red-orange, α, α' – Dipyridyl complex in aqueous medium.[8] To rule out carcinoma prostate if any, Prostate Specific Antigen (PSA) was estimated by ELISA methods in all the cases and controls.

STATISTICAL ANALYSIS

Data were analyzed by Statistical Package for Social Science (SPSS)–11.5 version. The comparison between patients and controls were done by student's '*t*' test and Pearson's correlation coefficient was applied to observe the correlation between variables.

RESULTS

The mean age of BPH patients and healthy controls was 67 ± 12 years and 63 ± 8 years respectively. The mean PSA level in serum of cases was 3.71 ± 1.56 ng/ml as compared to 1.61 ± 1.2 ng/ml in healthy controls which was not significant statistically.

Table 1 depicts the biochemical parameters in the patients of BPH and healthy controls. Plasma MDA, α-Tocopherol and Ascorbate in cases was 4.81 ± 1.87 nmol/ml, 0.85 ± 0.12 mg/dl and 0.93 ± 0.13 mg/dl compared to 3.69 ± 1.56 nmol/ml, 1.37 ± 0.31 mg/dl, 1.44 ± 0.38 mg/dl in healthy controls respectively and difference was significant statistically (<0.001). Plasma MDA level in the cases was elevated compared to controls. But there was significant decrease in vitaminic antioxidant α-Tocopherol and ascorbate in cases than controls as depicted in Table 1. Inverse correlation of plasma MDA with α-Tocopherol ($r = -0.09$, $p > 0.05$) and Ascorbate ($r = -0.51$, $p = 0.008$) was obtained in patients as shown in Figure 1 and 2 respectively.

Table 1. Comparison of different Biochemical parameters in BPH patients and healthy controls

Parameters	BPH Cases (Mean ± SD)	Controls (Mean ± SD)	P value
Malondialdehyde (nmol/ml)	4.81 ± 1.87	3.69 ± 1.56	<0.001
Tocopherol (mg/dl)	0.85 ± 0.12	1.37 ± 0.31	<0.001
Ascorbate (mg/dl)	0.93 ± 0.13	1.44 ± 0.38	<0.001

DISCUSSION

With advancing ages, the oxidative stress increases and may aggravate many pathological conditions including BPH in elderly man. The present study showed increased plasma MDA level, indicator of lipid peroxidation and decreased α-Tocopherol and ascorbate, the antioxidants status in the plasma of BPH patients. Increased MDA level is indicative of excessive lipid peroxidation in BPH signifying oxidative stress. The decrease of plasma antioxidants level indicates the imbalance between pro-oxidants and antioxidants status in favour of pro-oxidants. As a result, low level of α-Tocopherol and ascorbate in plasma are obtained with concomitant elevation of MDA level, as a marker of lipid peroxidation and oxidative stress. However there are few studies in this regard, which support this findings of elevated MDA level in BPH suggesting oxidative stress in BPH.[9]

There are studies showing decreased level of antioxidant enzymes in benign hyperplasia than non malignant prostate. Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPx) were decreased significantly in BPH patients than controls. With the decrease of GPx activity Catalase (CAT) alone was probably unable to detoxify H_2O_2 completely. An accumulation of H_2O_2 might occur resulting in higher production of OH· radical. The circulating antioxidant enzymes may be used up an the attempt to counteract the enhanced lipid peroxidation in the affected tissue.[10]

Plasma levels of α-Tocopherol and ascorbate of BPH patients were lower than the healthy controls in this study. The decrease in the levels of these non-enzyme antioxidants may be due to an attempt to scavenge the increased turnover of pro-oxidants, preventing oxidative damage in these patients, suggesting an increased defense mechanism playing against pro-oxidants. Two vitaminic antioxidants α-Tocopherol and ascorbate act in synergism in the membrane and cytosol of the cell. α-Tocopherol scavenges lipid peroxy free radicals and interrupts the chain reaction of lipid peroxidation becoming oxidized itself in the process. Ascorbate present in the aqueous compartments (e.g. cytosol, plasma and other body fluids) acts as a water soluble chain-breaking antioxidant, converts the tocopheroxyl radical back to active α-Tocopherol, there by replenishing antioxidant activity of α-Tocopherol.[11]

Ascorbate with glutathione is the first antioxidant to be depleted upon exposure to pro-oxidants producing environments either by directly scavenging these oxidants or trapping their intermediates. α-Tocopherol is the last to be depleted after bilirubin and uric acid. These

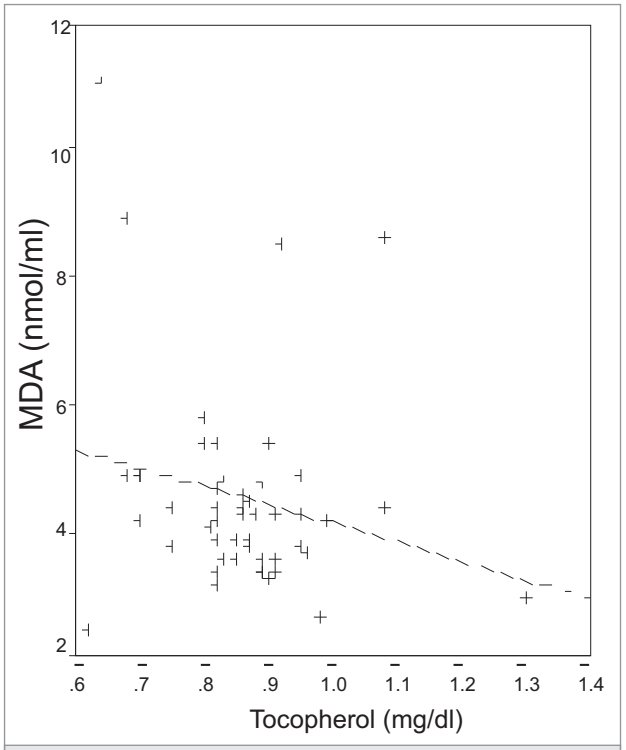

Figure 1. Scattered Diagram of MDA versus α-Tocopherol level showing their negative correlations.

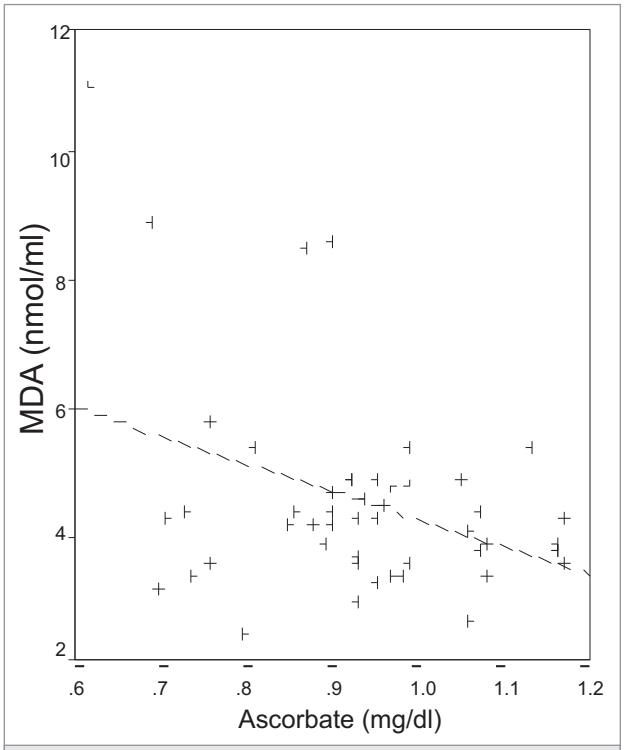

Figure 2. Scattered diagram of Plasma MDA versus Ascorbate level showing their negative correlations

antioxidants may act in a concert to protect tissues undergoing oxidative stress.[12] The present study showed a significant inverse correlation between MDA and ascorbate but correlation between MDA and α-Tocopherol was not significant statistically.

With the decrease of antioxidants in BPH, an accumulation of free radicals such as OH· might occur. These highly reactive oxidant molecules oxidize DNA, lipid and proteins and it reacts with various structures in the vicinity. Any oxidative lesion that is not repaired may lead to mutations, increasing the risk of carcinogenesis.[13] The enhanced lipid peroxidation occurs as consequence of the insufficient power of depleted antioxidant defense system for a prolonged duration. But whether the alteration in antioxidant status is a cause or a consequence of lipid peroxidation is still unclear.

In addition it has been suggested that antioxidants have protective role against BPH as well as progressive prostate cancer.[14] Thus, Ascorbate and α-Tocopherol supplementation may be helpful for enhancing prostate health of the ageing men. Thus, further research can be designed to see the outcome with the administration of Ascorbate and α- Tocopherol in patients with BPH and ageing male.

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