DISSERTATION SUBMITTED FOR THE MASTER'S DEGREE

IN

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TITLE

COMPARATIVE STUDY OF MALONDIALDEHYDE AND SUPEROXIDE DISMUTASE IN DIAGNOSED CASES OF BENIGN PROSTATIC HYPERPLASIA AND CONTROL SUBJECTS

SUBMITTED

BY

POORNIMA DUBEY

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DISSERTATION SUBMITTED

In partial fulfillment of the requirement for the award of degree of

Master of Science
In
Medical Biochemistry

By

POORNIMA DUBEY

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CERTIFICATE

This is to certify that **Miss Poornima Dubey**, student of M.Sc. Medical Biochemistry, Integral University has completed her dissertation titled "**comparative study of malondialdehyde and superoxide dismutase in diagnosed cases of benign prostatic hyperplasia and control subjects"** successfully**.** She has completed this work in the Department of Biochemistry, Integral Institute of Medical Sciences and Research, Integral University under my supervision. The dissertation was a compulsory part of her M.Sc. Degree.

I wish her good luck and a bright future.

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I wish her good luck and a bright future.

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Date : *Poornima Dubey*

Place: Lucknow

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LIST OF ABBREVIATIONS

BPH	Benign prostatic hyperplasia
OS	Oxidative Stress
MDA	Malondialdehyde
SOD	Superoxide dismutase
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
TBA	Thio barbituric acid
TBARS	Thio barbituric acid reactive substance
TCA	Tri chloro acetic acid
NBT	Nitroblue tetrazolium
PMS	Phenazine methosulphate
DNA	Deoxy ribonucleic acid
NO	Nitric oxide
WHO	World health organization
LPO	Lipid peroxidation
GSH-x	Glutathione peroxidation

INTRODUCTION

A prostate is a component of the male reproductive system. Fluid produced by the Prostate combines with semen. Protest fluid is particularly important for male fertility. Due to its irritating and obstructive symptoms in the urinary system, it is an incredibly frequent condition in older men (over 45 years of age) and has a distressingly high morbidity. BPH's pathophysiology and etiological origin are poorly understood (Ahmad et al., 2012).

The prevalence of BPH have been reported for different regions in previous studies **(Arafa et al., 2015; Egan et al., 2015; Lee et al., 2016; Speakman et al., 2015; Zhang et al., 2019),** the results varied substantially across studies and cannot be compared directly because of the inconsistencies of the diagnostic criteria of BPH, sampling methods and compositions of population studied between literatures. One study reported the burden of BPH at the global level based on the Global burden of disease 2017 study (**Launer et al., 2020**).

As people age, their bodies are under more oxidative stress, which can worsen any medical disease due to tissue damage and other consequence MDA, a sign of lipid peroxidation, was detected in higher concentrations while SOD, a marker of antioxidants, was found in lower concentrations in the blood of BPH patients, according to recent research. If antioxidant defence mechanisms are unable to scavenge increased lipid peroxidation, it might injure many human tissues.The decreasing level of antioxidants in the cell indicates that BPH is an oxidative stress-related disease. Few studies have been done that demonstrate elevated MDA levels in BPH, which may indicate oxidative stress **(Merendino et al., 2003).**

Prostate tissue damage and oxidative stress (OS) can lead to compensatory cellular Proliferation, resulting in hyperplastic growth. Inflammation of the prostate can generate free radicals and OS, such as inducible nitric oxide (NOS), reactive nitric species, and reactive oxygen species (ROS). White blood cells can produce free radicals, which can induce hyperplastic transformations through OS, affecting the tissue and DNA **(Chughtai et al., 2011**).

Vascular tissues, protein structures and activities, and genetic material can all be harmed by OS. Additionally, it may lead to posttranslational changes, such as those necessary for apoptosis and DNA repair (**Sciarra et al., 2008)**

Oxidative stress (OS) can indeed lead to oxidative DNA damage, resulting in various genomic alterations such as point mutations, deletions, or rearrangements. It can also hinder DNA repair mechanisms. Furthermore, OS can disrupt the balance between cell proliferation and cell death by modulating genomic alterations in cellular DNA. This disturbance in the normal regulation of programmed cell death can contribute to hyperplastic or precancerous transformations **(Hamid et al., 2011).**

The human prostate tissue is particularly susceptible to oxidative DNA damage due to its faster cell turnover and lower levels of DNA repair enzymes. When exposed to OS, the transcription factor NF-κB can be activated through the TNF-α/AP-1 transduction pathway and the NF-κB-inducing kinase (NIK) transduction pathway. NF-κB is recognized as a master inflammatory transcriptional regulator, and its targets include genes involved in immune response, inflammation, cell proliferation, cell migration, and apoptosis. Activation of NF-κB by OS in the prostate can have significant implications for the development and progression of prostate disorders (such as inflammation and cancer).The nuclear translocation of NF-κB can indeed activate target genes involved in carcinogenesis. It has been suggested that deregulation of NF-κB is a potential molecular mechanism underlying chronic inflammation and cancer development **(Hamid et al., 2011**).

When prostate epithelial cells are exposed to proinflammatory soluble mediators, NF-κB can be directly activated, leading to the local production of proinflammatory cytokines within the prostate epithelial cells **(Wong et al., 2009).**

In the normal prostate, the transduction pathway from NIK to NF-κB appears to be inactive. However, in benign prostatic hyperplasia (BPH), there is an increase in the TNF-α/AP-1

transduction pathway, followed by an increase in the apoptotic pathway, which acts to inhibit uncontrolled cell proliferation **(Hamid et al., 2011).**

Furthermore, a study demonstrated a novel connection between oxidative stress (OS) and loss of imprinting. It showed that OS, as measured by increased NF-κB activity, induces loss of imprinting of insulin-like growth factor 2 in both cancerous and noncancerous human prostate cells.

The loss of imprinting during aging plays a significant role in tumour development. Therefore, modulating NF-κB activity has the potential to prevent age-related epigenomic alterations **(Yang et al., 2014).**

Malondialdehyde (MDA) is an end product that results from the peroxidation of polyunsaturated fatty acids and related esters. Unlike free radicals, aldehydes such as MDA are relatively stable and can diffuse within or out of cells, attacking targets distant from the original site of free radical initiation. Additionally, MDA is not solely a reflection of lipid peroxidation but is also a by-product of cyclooxygenase activity in platelets. Persistent platelet activation is commonly observed in various clinical syndromes associated with enhanced lipid peroxidation. Therefore, measuring MDA levels in plasma or serum serves as a convenient in vivo indicator of lipid peroxidation. It is commonly used as a non-invasive biomarker of oxidative stress in clinical investigations of conditions related to radical-mediated physiological and pathological processes **(Meagher et al., 2000).**

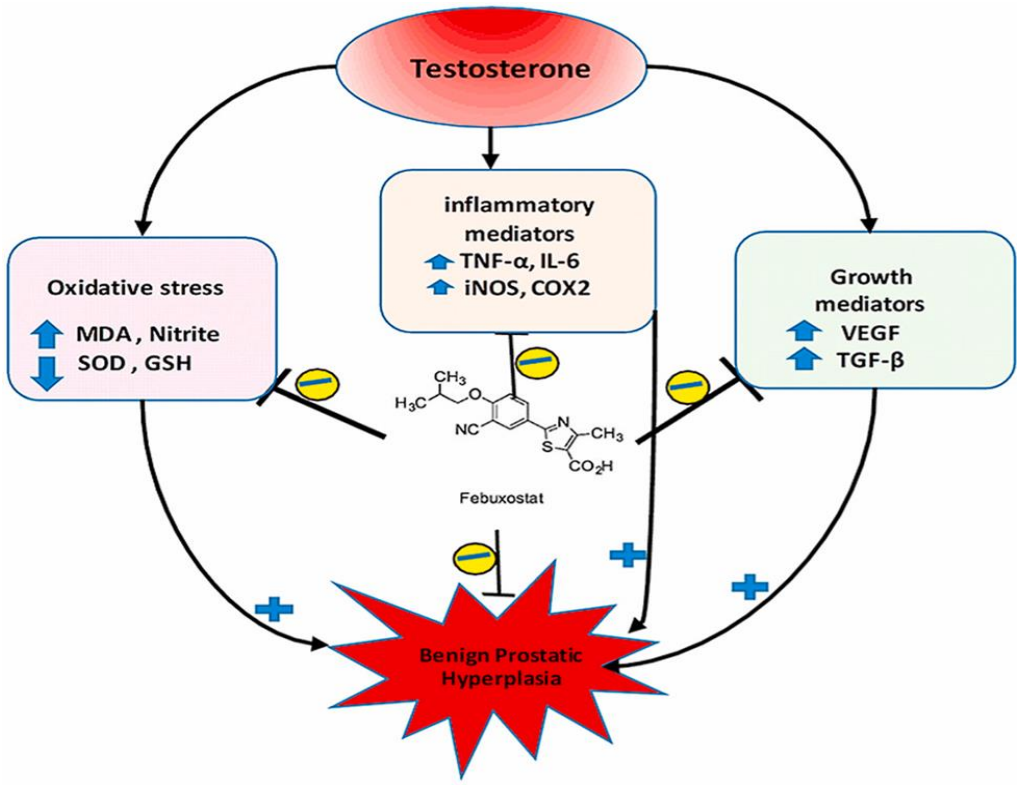

Figure:1. Schematic diagram presenting the proposed mechanisms of the febuxostat protective effects against testosterone-induced benign prostatic hyperplasia in rats

.**(Jena et at., 2016**).

A natural defence mechanism called the superoxide dismutase (SOD) enzyme system, along with vitamin C antioxidants such -as tocopherol and ascorbate, typically remove severely oxidative stressors. A reduction in the effectiveness of the antioxidant defence mechanisms may raise the severity of oxidative harm caused by ROS. The development of prostate tumours is also influenced by an imbalance between the MDA and SOD. **(Khandrika et al., 2009).**

Several studies have reported an increase in oxidative stress (OS) and a decrease in antioxidant mechanisms in prostate diseases. However, the data in this area are not consistent and definitive. In the majority of benign prostatic hyperplasia (BPH) tissues compared to the surrounding disease-free prostate tissue, lower activity of superoxide dismutase (SOD) and increased endogenous levels of DNA base products were found **(Olinski et al., 1995**). Furthermore, when SOD activity was

decreased in BPH tissues compared to normal tissues, the increase in DNA base products was more significant. On the other hand, when only SOD activity was decreased in BPH tissues, but catalase (CAT) activity remained similar in both tissue types, no changes in the levels of DNA base products were observed. These findings suggest a potential association between antioxidant enzyme activity and the levels of DNA base lesions in BPH tissues **(Olinski et al., 1995).**

Superoxide dismutase (SOD) is considered primary antioxidant enzymes, since it is involved in direct elimination of ROS. SOD protects cells against ROS produced during normal metabolism and after an oxidative influx. Antioxidant defense systems work cooperatively to alleviate the oxidative stress caused by enhanced free radicals.

The present study is designed to assess whole blood superoxide dismutase (SOD) activity and malondialdehyde (MDA) in benign prostatic hyperplasia patients (BPH) and healthy subjects.

REVIEW

OF

LITERATURE

A prostate gland that enlarges is known as benign prostatic hyperplasia, the most common ailment in older men, especially those over 50. Before the fourth international BPH consultation, LUTS was referred to as "prostatism." LUTS can be highly inconvenient, disrupting daily activities and reducing quality of life. (**Roehrborn et al., 1999**).

Men over the age of 40 are disproportionately impacted, and the disease's frequency rises with age to the point where 90% of men in their 80s are affected (**McNeal et al., 1968).**

Epidemiology

Benign prostatic hyperplasia is a prevalent urological disease that primarily affects older men worldwide. However, there is a lack of comprehensive data regarding its global, regional, and national burden, as well as its trends over time. To address this gap, the **Global Burden of Diseases,** Injuries, and Risk Factors Study (GBD) 2019 conducted an estimation of the prevalence and global trends of benign prostatic hyperplasia.

In 2019, the global prevalence of benign prostatic hyperplasia was estimated at 94.0 million cases (95% UI 73.2 to 118), compared to 51.1 million cases (43.1 to 69.3) in 2000. The age-standardized prevalence of the condition was approximately 2480 (1940 to 3090) cases per 100,000 people. While the total number of prevalent cases increased by 70.5% (68.6 to 72.7) between 2000 and 2019, the global age-standardized prevalence remained relatively stable (-0.770% [-1.56 to 0.0912]).The age-standardized prevalence of benign prostatic hyperplasia varied across regions in 2019, ranging from 6480 (5130 to 8080) cases per 100,000 in Eastern Europe to 987 (732 to 1320) cases per 100,000 in north Africa and the Middle East.

When analysing disability-adjusted life-years (DALYs), all five socio-demographic index (SDI) quintiles observed an increase in the absolute DALY burden between 2000 and 2019. The middle

SDI quintile experienced the most significant increase (94.7% [91.8 to 97.6]), followed by the low-middle SDI quintile (77.3% [74.1 to 81.2]) and the low SDI quintile (77.7% [72.9 to 83.2]).

The age-standardized DALY rates showed minimal changes overall, with slight increases observed in the three lower SDI quintiles (low, low-middle, and middle) and small decreases in the two higher SDI quintiles (high and high-middle SDI) **(Awedew et al., 2019).**

Apoptosis, or programmed cell death, is a protective mechanism in the body that helps eliminate defective cells and prevent their accumulation and spread. However, it has been observed that senescent cells, both in vitro and in vivo, exhibit decreased susceptibility to apoptosis induced by oxidative stress **(Muradian et al., 2001**).

Highly reactive aldehydes, such as 4-hydroxynonenal and MDA, which are products of lipid peroxidation, have the ability to modify DNA and proteins. This can lead to mutagenic, genotoxic, and cytotoxic events. Therefore, elevated levels of MDA and other reactive aldehydes may explain the DNA base modifications observed not only in prostate cancer but also in the epithelium of benign prostatic hyperplasia (BPH).

In a study, it was found that MDA levels strongly correlated with prostate-specific antigen (PSA) levels in BPH patients. PSA is a useful parameter for diagnosing prostate cancer and determining the malignant potential of recurrent tumours after radical prostatectomy. PSA values are also increased in BPH. The strong positive correlation between MDA and PSA levels suggests that elevated circulating MDA levels could serve as a marker of lipid peroxidation and inflammation in the prostate epithelium. Additionally, very high MDA levels in a BPH patient may be indicative of a higher risk for prostate cancer (**Muradian et al., 2001**).

Risk factor of BPH

In the development of BPH, various risk factors, beyond the direct hormonal effects of testosterone, play a significant role.

AGE:- Age is a significant factor influencing the prevalence of BPH. Studies conducted through autopsies have shown that the histological prevalence of BPH increases with age.

Specifically, the prevalence has been observed to be 8% in the fourth decade of life, 50% in the sixth decade, and 80% in the ninth decade [12]. Numerous observational studies conducted in Europe, the United States, and Asia have also demonstrated that older age is a risk factor for the onset and clinical progression of BPH, as measured by various metrics.

(Barry et al., 1997).

Race:- The association between race and the risk of benign prostatic hyperplasia (BPH) remains unclear, as no consistent patterns have emerged. Observational studies comparing men of different races, including black, Asian, and white men, have produced variable results. Studies conducted in the United States have observed that black men tend to have larger prostate transition zone and total volume compared to white men. However, large analyses of the US Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and the Health Professionals Follow-Up Study have found no differences in the clinical risk of BPH between black and white men. **(Fowler et al., 1999).**

Lifestyle:- There is a growing recognition that modifiable lifestyle factors have a significant impact on the progression and development of benign prostatic hyperplasia (BPH).

Diet: - Various studies suggest that both macronutrients and micronutrients may have an impact on the risk of developing benign prostatic hyperplasia (BPH), although the findings are not consistent across all studies. In terms of macronutrients, there is evidence to suggest that increased intake of total energy, energy-adjusted total protein, red meat, fat, milk and dairy products, cereals, bread, poultry, and starch may potentially increase the risks of clinical BPH and BPH surgery. On the other hand, consumption of vegetables, fruits, polyunsaturated fatty acids, linoleic acid, and vitamin D has been associated with a potential decrease in the risk of BPH. **(Parsons et al., 2007)**

Obesity:- Research consistently indicates that higher levels of adiposity are positively linked to increased prostate volume. This means that as adiposity increases, so does the size of the prostate.

Multiple studies conducted across various populations have shown a positive association between body weight, body mass index (BMI), waist circumference, and prostate volume **(Parsons et al., 2006).**

Genetic predisposition: - Cohort studies have provided evidence of a genetic predisposition to benign prostatic hyperplasia (BPH). In one study, first-degree relatives showed a four-fold increase in the risk of BPH compared to the control group. This suggests a familial link in the development of BPH (**Lawrentschuk. et al., 2021**). Twin studies have further supported these findings by demonstrating consistent results in the disease severity of BPH among monozygotic twins, with higher rates of lower urinary tract symptoms (LUTS) observed **(Rohrmann, S., et al.,2016).**

Pathophysiology

The development of lower urinary tract symptoms (LUTS) and bladder outlet obstruction in men with benign prostatic hyperplasia (BPH) can be attributed to both static and dynamic factors (**Caine, M. 1986**). Static obstruction occurs as a direct result of prostate enlargement, which leads to compression of the per urethral region and obstruction of the bladder outlet. The compression requires increased voiding pressures to overcome the resistance to urine flow. Additionally, prostate enlargement distorts the bladder outlet, further contributing to flow obstruction **(Foo, K. T. 2017).**

Dynamic factors involve the tension of the smooth muscle in the prostate. This is why medications like 5-alpha reductase inhibitors are used to reduce prostate volume and alpha-blockers are used to relax smooth muscle. The tension in the smooth muscle plays a role in the pathophysiology of BPH-related symptoms **(Lepor et al., 2005**).

In men with BPH, there are reductions in the elasticity and collagen content of the prostatic urethra. These changes in elasticity and collagen may worsen bladder outlet obstruction by decreasing compliance (flexibility) and increasing resistance to urine flow. These dynamic factors may help explain why prostate size alone is not always a reliable predictor of disease severity in BPH (**Babinski et al., 2014**).

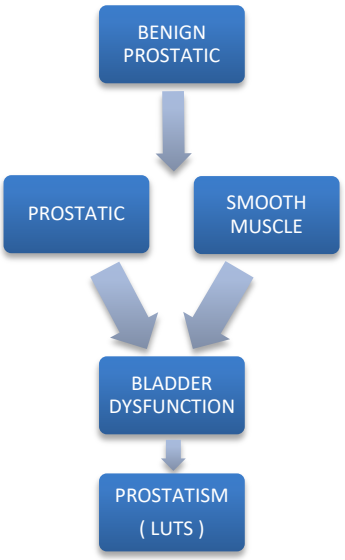

Fig:2. Pathophysiology of Benign Prostatic Hyperplasia **(Lepor et al.,. 2005).**

Diagnosis of Benign prostatic hyperplasia

A variety of essential diagnostic tools and investigations are employed to diagnose benign prostatic hyperplasia (BPH) in men who experience lower urinary tract symptoms (LUTS).

Physical examination: - A thorough physical examination should be conducted, with specific attention given to the urinary tract. The healthcare provider should examine the suprapubic region to identify any indications of bladder distension. Additionally, the penis should be carefully inspected for signs of phimosis, meatal stenosis, or abnormal penile lesions that may contribute to lower urinary tract symptoms (LUTS) **(Gravas, S. 2015).**

Urinalysis: - Urinalysis is an essential diagnostic test that involves collecting a urine sample for analysis. It helps identify substances in the urine associated with metabolic disorders, renal dysfunction, or urinary tract infections. According to the guidelines provided by the European Urological Association, although the evidence supporting urinalysis is limited, experts generally agree that the benefits of using it outweigh the associated costs. Therefore, it is recommended to include routine urinalysis, which can be performed through dipstick analysis or microscopic evaluation, as part of the initial evaluation for a patient presenting with lower urinary tract symptoms (LUTS) **(Chughtai et al., 2016).**

Prostate-specific antigen (PSA) test: - The prostate-specific antigen (PSA) test is utilized to measure the level of PSA, which has been demonstrated to correlate with prostate volume **(Cher et al., 1996)**

Renal function: - If there is a suspicion of renal impairment, it is necessary to assess renal function by measuring the levels of serum creatinine or estimating the glomerular filtration rate (GFR). These diagnostic tests are crucial for evaluating renal health **(Gravas et al., 2015).**

Urinary tract imaging: - While routine upper tract imaging is not recommended for patients with benign prostatic hyperplasia (BPH), there are certain circumstances where it may be necessary. These include patients who present with urinary tract infection, urolithiasis (urinary stones), renal insufficiency, and/or hematuria (blood in urine). In such cases, urinary tract imaging becomes essential for a comprehensive evaluation **(Chughtai, et al., 2016).**

Oxidative stress

Helmut Sies1 originally introduced the term "oxidative stress" to describe an imbalance between the production of oxidants and the protective actions of antioxidants, potentially leading to damage in biological systems (Sies, H., et al 1985). Over time, the field of redox biology has progressed from focusing solely on oxidative stress in pathological conditions to encompassing

the broader concept of redox signaling in physiological processes. This evolution has broadened our understanding of the intricate role played by redox signaling in various physiological contexts (Flohé et al., 2020) (Sies et al., 2017).

Extensive research has demonstrated that oxidants play a role in the development of diverse diseases, such as atherosclerosis, chronic obstructive pulmonary disease (COPD), Alzheimer's disease, and cancer. These studies have revealed numerous mechanisms through which oxidants contribute to cellular damage.

Nevertheless, the degree to which oxidative stress contributes to the pathology of different diseases varies significantly. Consequently, the effectiveness of augmenting antioxidant defenses may be restricted in certain diseases, as simply increasing antioxidant levels may not be sufficient to mitigate the underlying damage **(Pham-Huy et al., 2008).**

Roles of oxidative stress in disease

Oxidative stress contributes to disease through two primary mechanisms. The first mechanism involves the generation of reactive species, including hydroxyl radicals (•OH), peroxynitrite ($ONOO^-$), and hypochlorous acid (HOCl), during oxidative stress. These reactive species directly oxidize macromolecules such as membrane lipids, structural proteins, enzymes, and nucleic acids. Consequently, cellular function is disrupted, leading to cell dysfunction and death.

The second mechanism of oxidative stress involves aberrant redox signalling. Under normal physiological conditions, cells generate hydrogen peroxide (H_2O_2) as a second messenger in response to stimulation. However, in oxidative stress, the non-physiological overproduction of H_2O_2 can lead to deregulated redox signalling, causing cellular signalling pathways to malfunction.

It is important to note that both types of oxidative stress mechanisms can coexist within a single disease, contributing to its pathology **(Sies et al., 2017).**

Oxidative stress in benign prostatic hyperplasia

The development of benign prostatic hyperplasia (BPH) is thought to involve various factors, including inflammatory mediators, hormones, dietary factors, inflammatory genes, and oxidative stress (OS). Among these, oxidative stress and damage to prostate tissue are believed to contribute to compensatory cellular proliferation, ultimately leading to hyperplastic growth in the prostate.

Prostatic inflammation can stimulate the generation of free radicals within the prostate. The extent of oxidative damage can be further aggravated by a reduced efficiency of antioxidant defense mechanisms. The delicate balance between oxidative stress (OS) and the antioxidant component also plays a significant role in the development of prostate diseases. Multiple studies have demonstrated the involvement of oxidant products and the depletion of antioxidant substances in patients with benign prostatic hyperplasia (BPH). It is widely accepted that free radicals contribute to the process of carcinogenesis, and BPH is considered a premalignant condition with the potential to progress into prostate cancer. Notably, prostate cancer patients exhibit higher levels of OS markers and lower antioxidant activity compared to individuals with BPH and healthy controls **(Pac et al., 2010).**

Malondialdehyde (MDA)

Malondialdehyde is an organic compound represented by the formula CH2(CHO)2, and it is produced as a byproduct of lipid metabolism within the body. As a highly reactive compound, malondialdehyde is among the reactive electrophile species that induce cellular toxic stress and form covalent protein adducts known as advanced lipid oxidation end products (ALE). Additionally, when malondialdehyde reacts with deoxyadenosine and deoxyguanosine in DNA, it can generate mutagenic DNA adducts. It is worth noting that malondialdehyde is present in various foods and is particularly abundant in rancid food products **(Merendino et a.,l 2003).**

Antioxidant

Antioxidants are substances that impede oxidation, a chemical reaction that can generate free radicals and trigger chain reactions that harm cellular structures in organisms. Antioxidants, including thiols and ascorbic acid (vitamin C), halt these chain reactions. To maintain a balanced oxidative state, both plants and animals possess intricate networks of overlapping antioxidants. These include internally produced antioxidants like glutathione and enzymes such as catalase and superoxide dismutase, as well as dietary antioxidants like vitamins C and E **(Pawar et al., 2016).**

Superoxide dismutase (SOD)

Superoxide dismutase (SOD) represents a group of metalloenzymes present in all living organisms. They play a crucial role in defending against the harmful effects of reactive oxygen species (ROS) **(Kangralkar et al., 2010).** These enzymes are at the forefront of protecting cells from damage caused by excessive levels of the superoxide anion free radical (O2 -). SODs facilitate the dismutation of O2 into molecular oxygen and hydrogen peroxide (H2 O2), effectively reducing the concentration of O2 and preventing cellular **harm (Yasui, K., & Baba, A. (2006) (Mccord, et al., 1993)**. During this process, the metal ions in the active site of SOD undergo alternate oxidation and reduction reactions.

Classification of SOD

SODs can be classified into four distinct groups based on the metal cofactors present in their active sites. These groups include-

(i) Copper-Zinc-SOD (Cu, Zn-SOD),

(ii)Iron SOD (Fe-SOD),

(iii)Manganese SOD (Mn-SOD),

(iv) Nickel SOD.

Each group is characterized by the specific metals involved in their catalytic activity.

The distribution of these different forms of SODs varies across biological kingdoms, and they are found in different subcellular compartments. Their distribution is not uniform, and different organisms may have different types of SODs in different cellular locations. This variability highlights the diverse strategies employed by organisms to cope with ROS and protect against oxidative damage **(Youn et al., 1996).**

MDA and SOD level in BPH patients

The development of prostate hyperplasia has been linked to various mechanisms, including oxidative stress (OS), inflammatory mediators, hormonal factors, enzymatic factors, dietary factors, inflammatory genes, and the Gleason score grading system, which is used to assess the prognosis of prostate cancer (PCa) **(Awodele et al 2011).**

Oxidative stress (OS) is believed to play a significant role in prostate hyperplasia. It refers to an imbalance between the production of reactive oxygen species (ROS) and the ability of cells to counteract their harmful effects (Jones et al., 2007). Inflammatory mediators and genes also contribute to the development of prostate hyperplasia, further exacerbating the oxidative stress **(El Gaafary, M., et al 2015).**

Hormones, particularly androgens, can influence oxidative stress levels by altering intracellular glutathione levels and the activity of detoxification enzymes such as gamma-glutamyl trans peptidase. Changes in hormonal levels can disrupt the cellular prooxidant-antioxidant balance, leading to increased oxidative stress **(Shankar et al., 2015).**

Additionally, enzymatic factors, dietary factors, and the Gleason score grading system, which is a prognostic tool for PCa, have been implicated in prostate hyperplasia **development (Almushatat et al., 2006).**

Reactive nitrogen species (RNS) and ROS are by products of normal cellular metabolism and have an impact on cell signalling. Elevated levels of ROS and RNS can induce oxidative

stress, prompting cells to activate various mechanisms to cope with these changes (Li et al., 2014). It's important to note that these mechanisms are not mutually exclusive, and prostate hyperplasia is likely influenced by a combination of these factors **(Gaafary et al., 2015)**.

Although several studies have been conducted on this topic, the relationship between oxidative stress and BPH is still unclear. In particular, there are limited studies that have focused on the role of MDA and SOD in BPH patients. To the end, this study is aimed

at assessing the correlation between malondialdehyde (MDA) and Superoxide dismutase (SOD) in the development and severity of BPH.

AIM

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OBJECTIVES

AIM:-

The aim of the study is to find an association between malondialdehyde (MDA) and Superoxide dismutase (SOD) in diagnosed cases of benign prostatic hyperplasia and control subjects.

OBJECTIVES:-

1. To determine the level of malondialdehyde (MDA) in diagnosed cases of benign prostatic hyperplasia patients and control subjects.
2. To determine the activity of Superoxide dismutase (SOD) in diagnosed cases of benign prostatic hyperplasia patients and control subjects.

3. To determine the correlation of malondialdehyde and superoxide dismutase in diagnosed cases of benign prostatic hyperplasia patients and control subjects.

MATERIALS

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METHODS

Research Question:

Is there any association between malondialdehyde and Superoxide dismutase in benign prostatic hyperplasia patients and Control subjects?

Statistical Hypothesis

Null Hypothesis (H_0): There is no significant difference between level of malondialdehyde and Superoxide dismutase in diagnosed cases of benign prostatic hyperplasia patients and control subjects.

Alternate Hypothesis (H_1): There is a significant difference between levels of malondialdehyde and Superoxide dismutase in diagnosed cases of benign prostatic hyperplasia patients and control subjects.

Study Design: -Prospective

Type of study:- A Case-Control Study

Sampling Method:-Non-probability, Purposive sampling.

Place of study: Department of Biochemistry, Integral Institute of Medical Science and research, Lucknow (U.P).

Collaborating department: - Department of General Surgery, OPD at IIMS&R, Integral University, Lucknow.

Enrolment of participants: Cases will be enrolled from the benign prostate hyperplasia attending the Integral Hospital. Controls will be enrolled from the general population.

Study period: - 6 months

Data collection

A detailed clinical history including age, occupation, socio-economic status, and any associated risk factors contributing to the illness was elicited from BPH patients and control subjects.

SUBJECT SELECTION:-

Selection for control

1. Apparently healthy individuals
2. Age of 45 years and above
3. Individuals who have agreed to sign the consent form

SELECTION OF CASE:-

Inclusion Criteria:-

1. Diagnosed cases of BPH
2. Age of 45 years and above
3. Patients who have agreed to sign the consent form

Exclusion Criteria:-

1. Patient with history of chronic disease.

2. Subjects taking antioxidants.

SAMPLE COLLECTION

Collection of samples: -Under the aseptic condition 4 ml of venous blood was collected in the plain vial and EDTA vial from the subject. The blood sample allowed to clot at room temperature for 15 minutes. The sample was centrifuged 1000 rpm/min for 10 minutes to separate the serum.

- 0.8 ml of serum was used for estimation of MDA in plain vial.
- 0.02ml of blood was used for estimation of SOD in EDTA vial.

STORAGE OF SAMPLES

The serum samples for the estimation of MDA and SOD was stored at -20^0 C unit testing in Central clinical laboratory, Department of biochemistry, IIMS&R, and Lucknow (U.P).

SAMPLE SIZE ESTIMATION

$$n = \left(\frac{r+1}{r}\right)\frac{\sigma^2(Z_\beta + Z_{\alpha/2})^2}{(d\text{ifference})^2}$$

(Charan, J., & Biswas, T. 2013)

n = sample size in the case group.

r = ratio of controls to cases.

σ = standard deviation of the outcome variables.

difference = effect size (the difference in means of cases and controls).

$Z\beta$ = Represent the derived power (typically for 80% power).

$Z\alpha_{/2}$ = Represents the derived level of statistical for 95% CI.

$Z\alpha_{/2}$ = 1.96, For 80% power $Z\beta$ = 0.84.

Mother article -Ahmad, M., Suhail, N., Mansoor, T., Banu, N., & Ahmad, S. (2012). Evaluation of oxidative stress and DNA damage in benign prostatic hyperplasia patients and comparison with controls. Indian journal of clinical biochemistry: IJCB, 27(4), 385–388.

Expected mean difference between cases and controls is **0.26**

Standard Deviation (**σ**) is **0.40**

N1 (Cases) = ***30***

N2 (Control) = ***30***

LABORATORY INVESTIGATION:

1. Determination of Malondialdehyde, MDA, by Satoh K. (1978) method.

Principle: - Deproteinized serum is treated with Thiobarbituric acid (TBA) at 90°c for about 10 minutes giving a pink color product. This gives a determination of the TBA reactive substance measured at 535 nm on a spectrophotometer.

Reagents

1. Trichloroacetic Acid (TCA)
2. Thiobarbituric Acid (TBA)
3. 0.25N Hydrochloric Acid
4. 1N Sodium Hydroxide
5. Tetramethoxypropane

MDA Procedure

0.8 ml of serum + 1.2 ml of TCA-TBA-HCl Reagent

↓

Mix and keep in a boiling water bath for 10 minutes

↓

Cool and add 2 ml of NaOH

↓

O.D is taken at 535 nm against a blank which contains normal saline in place of serum.

Calculations

$$\text{Sample (nmol/ml)} = \frac{Absorbance\ of\ Sample}{Absorbance\ of\ Standard} \times 10$$

2. Estimation of SOD by using Nitroblue tetrazolium (NBT) method (McCord et al., 1969).

Principle: NADH in the presence of Phenazine methosulphate (PMS) generate superoxide radical. This oxygen free radical reduces the nitroblue tetrazolium (NBT) and form farmazon having dark blue color. When SOD source is added to above reaction mixture this participate another reaction to neutralize O_2^- in to H_2O_2 and therefore first reaction; the reduction of NBT, slowed down and give a measure of SOD activity in test sample.

Reagents:

1. Sodium pyrophosphate buffer- 909 mg/dl in TDW pH 8.2
2. Nitroblue Tetrazolium – 12.80 mg/10 ml in above buffer
3. NADH – 16.59 mg/10 ml in above buffer
4. Phenazine methosulphate – 2.8 mg/100 ml TDW

Experimental procedure:

1. The blood lysate was used as enzyme source.

2. Two reaction setups were run in parallel.

3. The tubes in first setup (experimental) received 0.2 ml NBT, 0.2 ml PMS, 1.1 ml pyrophosphate buffer and 20 µl enzyme source.

4. The tubes in second setup (reference) received all the above reagents except the enzyme source.

5. The reaction started simultaneously in both sets by the addition of 0.2 ml NADH.

6. After 90 seconds interval, 1.0 ml glacial acetic acid was added to each tube for checking the reaction.

7. Then 20 µl enzyme sources were added in the reference tubes. The absorbance of these tubes was read at 560 nm against reagent blank.

Difference between reference and experimental OD (net OD) gives the inhibition of NBT reaction by enzyme source. Protein was also estimated in the enzyme source. The unit of SOD enzyme activity was defined as the amount of enzyme required to inhibit the optical density at 560 nm of NBT reduction by 50% in one minute under the assay condition. The results were expressed as U/mg protein.

Calculation

SOD Activity=Unit/mg of protein

01 Unit Enzyme activity = 50% NBT reduction per minute

ETHICS REVIEW

Permission from the Integral University ethics committee was taken (IEC/IIMS&R 2023/69)

STATISTICAL ANALYSIS PLAN

Statistical analysis was performed using Graph Pad software and Microsoft – Excel. All the data was expressed as mean ± standard deviation. An unpaired t-test was performed to compare the study parameters between cases and controls. Karl Pearson's correlation analysis was employed to determine the relationship between variables. P-value <0.05 was considered statistically significant.

OBSERVATIONS

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RESULTS

Age and BMI in BPH -

In this study, 30 control Subjects aged 40 years and above along with 30 benign prostate hyperplasia (BPH) patients were included. The mean age of control subjects (50.56 ±3.67) and BPH patients (50.16 ±6.29) have been found not statistically significant, And the mean of BMI control subjects (27.43 ±3.54) and BPH patients (27.53 ±3.72) have been found not statistically significant (Table. 1)

Table: 1 Age and BMI wise distribution of controls and cases.

Parameters	**N**	**Controls (Mean / ±SD)**	**Cases (Mean / ±SD)**	**p-value**	**Significance**
Age (Years)	30	50.56 ±3.67	50.16 ±6.29	0.8536	Not statistically significant
BMI (kg/m^2)	30	27.43 ±3.54	27.53 ±3.72	0.915	Not statistically significant

N= Number of cases or controls, $p<0.05$ significant

MDA and SOD -

Results showed that mean of MDA was found significantly elevated in cases as compared to controls ($p<0.001$). However, mean of SOD was found significantly reduced in cases as compared to controls ($p<0.001$), shown in (Table 2.)

Table: 2 Mean and standard deviation of the MDA and SOD in cases and controls.

MDA and SOD (µmol/L)				
Variables	**Controls Mean ±SD (N=30)**	**Cases Mean ±SD (N=30)**	**p-value**	**Significance**
MDA (µmol/L)	1.24±0.29	3.06±0.32	**<0.001***	Statistically significant
SOD (U/mg of protein/min)	6.98±0.86	0.87±0.30	**<0.001***	Statistically significant
**. Correlation is significant at the 0.05 level (2-tailed).* *Data represented as Mean* ±SD				

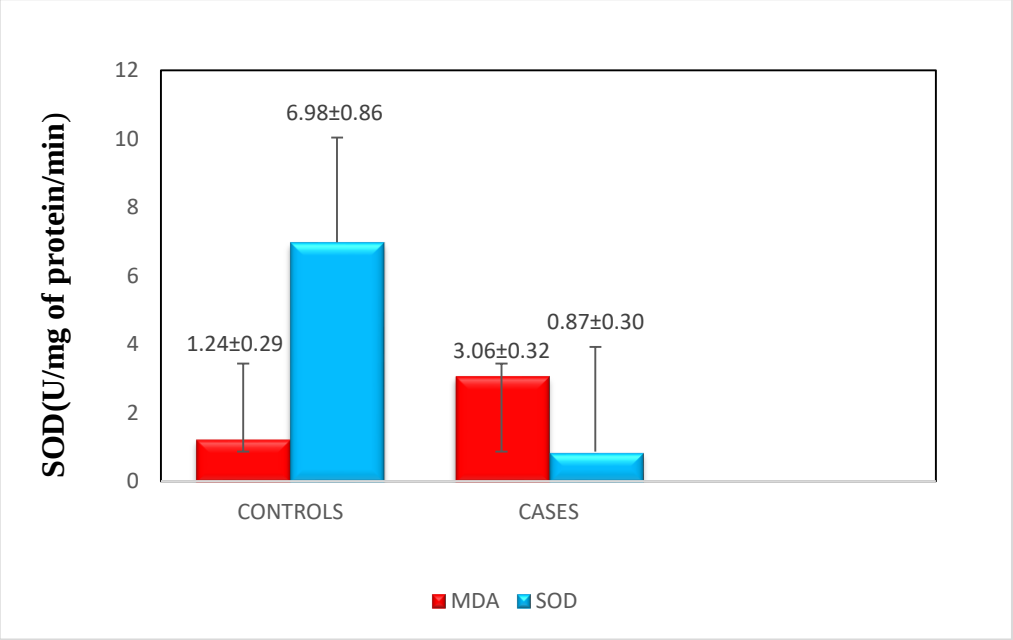

Figure: Comparison of MDA and SOD in cases and controls.

Karl Pearson's correlation coefficient among thestudy parameters in cases

Results showed that MDA has a significant negative correlation with SOD among cases (r = -0.431, p<0.05), shown in (Table: 3)

Table 3: Pearson Correlations Analysis among Cases		
Variables		**SOD (U/mg of protein/min)**
MDA (µmol/L)	Pearson Correlation	**-0.431***
	Sig. (2-tailed)	.017
	N	30
**. Correlation is significant at the 0.05 level (2-tailed).* *N= Number of cases* *MDA: Malondialdehyde, SOD: Superoxide dismutase*		

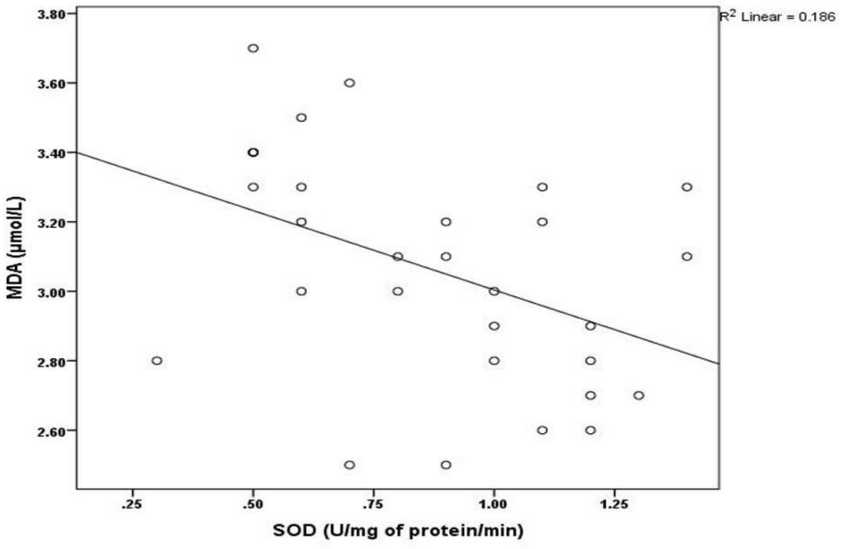

Figure- Scatter diagram showing correlation between MDA and SOD.

DISCUSSION

Excessive production of free radicals can cause direct damage to various biological molecules such as DNA, proteins, lipids, and carbohydrates through a process called oxidation. In this study we observed that the malondialdehyde concentration was significantly increased in BPH individuals (3.06±0.32) compared to Controls(1.24±0.29).This finding is a agreement there with **(Margaritis, I., et al., 2003)** who has reported that the MDA concentration is increased in BPH individuals compared to control group and was found to be statically significant.

Free radicals are highly reactive molecules that contain unpaired electrons, and when they interact with these biological molecules, they can cause oxidative damage. One of the secondary effects of excessive free radical production is the generation of metaboslites during lipid oxidation, a process known as lipid peroxidation. Lipid peroxidation leads to the formation of various products, including aldehydes, with one of the most studied and commonly measured aldehydes being malondialdehyde **(Margaritis, I., et al., 2003).**

MDA is particularly noteworthy because of its high cytotoxicity and inhibitory action on antioxidant enzymes. Cytotoxicity refers to the ability of a substance to cause damage or death to cells, and MDA has been shown to exhibit such properties. Additionally, MDA can interfere with the activity of antioxidant enzymes, which are responsible for neutralizing free radicals and protecting cells from oxidative damage. By inhibiting antioxidant enzymes, MDA can further contribute to the accumulation of free radicals and oxidative stress. The combined effects of the cytotoxicity of MDA and its inhibitory action on antioxidant enzymes make it capable of acting as a cancer promoter and a carcinogenic agent. Cancer promotion refers to the stimulation or enhancement of the growth and development of cancer cells, while carcinogenic agents are substances that, in combination with a carcinogen, increase the likelihood of developing cancer **(Sheeja et al ., 2006).**

In our study of blood samples from patients with benign prostatic hyperplasia (BPH), we observed a significant decrease in the enzymatic activity of cytosolic SOD in cases (8.47±1.33) as compared to controls (6.98±0.86) respectively. This decline in SOD activity can be attributed to the response of the body to moderate levels of superoxide anions present in these cells, which involves the up regulation of SOD **(Pincemail et al., 2002).** Research conducted by Jung et al. (1997) has shown that the decrease in SOD enzymatic activity in benign prostatic hyperplasia is associated with an increase in the accumulation of modified DNA bases.

The superoxide dismutase (SOD) enzyme plays a crucial role in the antioxidant defence mechanism by directly eliminating reactive oxygen species (ROS). It achieves this by catalysing the dismutation of the superoxide radical (O2-) into hydrogen peroxide (H_2O_2), thereby reducing the toxic effects caused by this radical and other radicals generated from subsequent reactions **(Pasupathi, et al., 2009).**

The study also showed a correlation between MDA concentration and Age, further solidifying the fact that in the age-related BPH, OS plays a crucial role in disease progression. According to our data, though the research project was conducted in case and control patients of the same age group 50.16±6.29 for cases and 50.56±3.67 for control, there was a significant change in OS levels.

The data further suggests that Age is not a factor in the antioxidant functioning. Antioxidant role and efficiency is not dependent on age but rather dependent on the OS levels exerted on a body. Oxidative stress significantly affects antioxidant performance.

SUMMMARY

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CONCLUSIONS

SUMMMARY

The present study was designed to compare to MDA and SOD levels in diagnosed benign prostatic hyperplasia patients and healthy controls

Estimated parameters were:

- Malondialdehyde (MDA)
- Superoxide Dismutase (SOD)

The levels of the aforementioned parameters were compared between the cases and control groups. The observation made in the study was as follows:

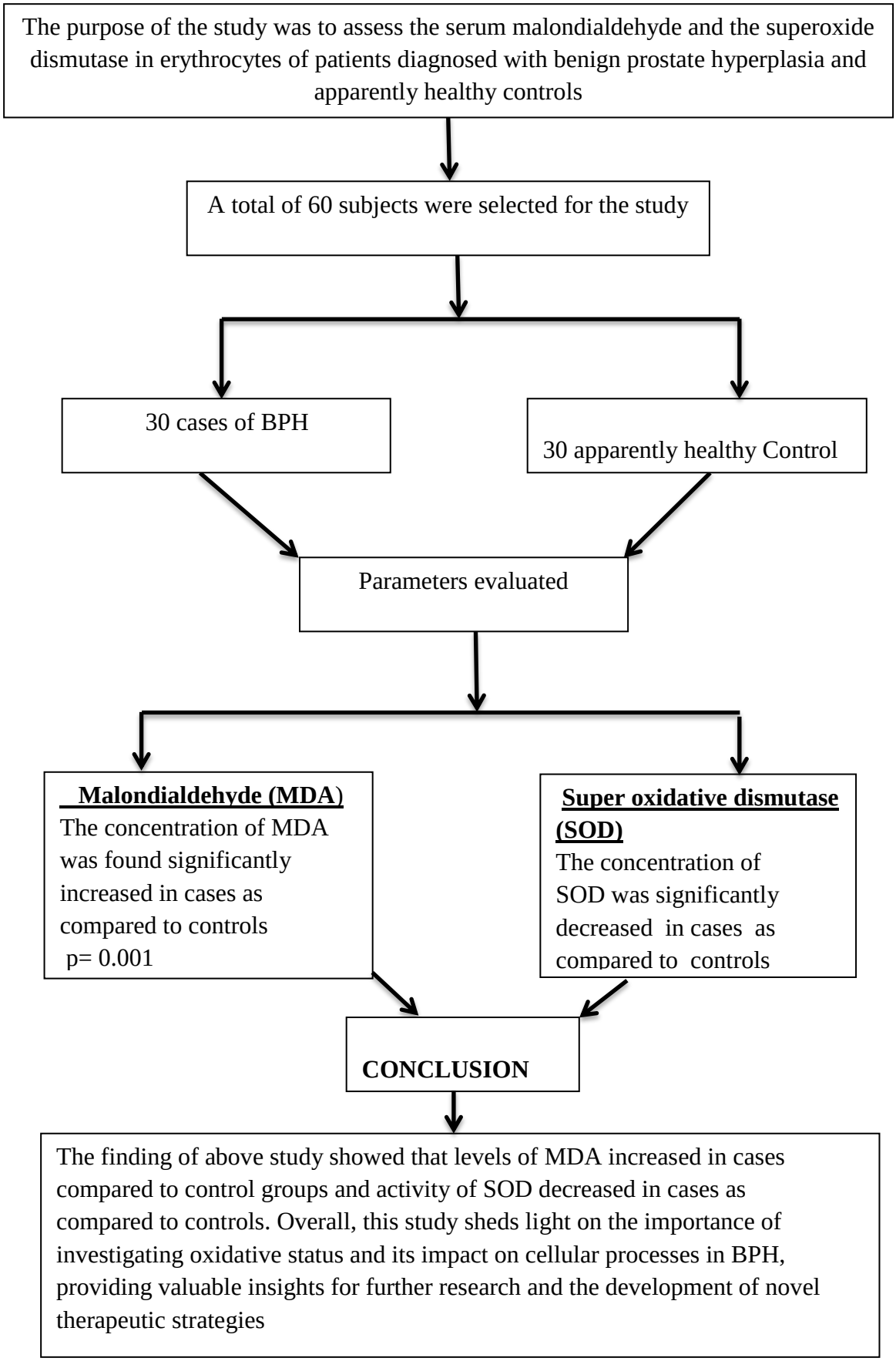
- The mean age of the control group was 50.56 ±3.67 years while the mean age of the cases was 50.16 ±6.29 years. No significant difference was found in mean ages between the groups (0.8536).
- The mean MDA levels of the control group was 1.24±0.29 while the mean MDA levels of the cases was 3.06±0.32(μmol/L). Significant difference was found in mean MDA levels between the groups (<0.001).
- The mean SOD activity of the control group was 6.98±0.86 while the mean SOD activity of the cases was 0.87±0.30(U/mg of protein/min). Significant difference was found in mean SOD activity between the groups (<**0.001**).

CONCLUSIONS

This study provides evidence that the pathophysiology of benign prostate hyperplasia (BPH) is accompanied by an impaired oxidative status, which manifests as elevated levels of malondialdehyde (MDA), depletion of antioxidant activity, and decreased enzymatic activities of superoxide dismutase (SOD.

Overall, this study sheds light on the importance of investigating oxidative status and its impact on cellular processes in BPH, providing valuable insights for further research and the development of novel therapeutic strategies.

FLOW CHART OF RESEARCH WORK



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Unique Identification No

INTEGRAL INSTITUTE OF MEDICAL SCIENCES AND RESEARCH LUCKNOW -226026

INCLUSION AND EXCLUSION CRITERIA – FOR CASES

Inclusion Criteria

S.N.	Criteria	YES	NO
1.	Diagnosed case of benign prostate hyperplasia		
2.	Age of 40 years and above		
3.	Patients who have agreed to sign the consent form		

Exclusion Criteria

S.N.	Criteria	YES	NO
1.	History of any chronic disease		

Subject is eligible for the study, if all **INCLUSION** criteria are **YES** and all **EXCLUSION** criteria are **NO**.

INVESTIGATOR STATMENT:

I have verified the data entered in the case report form and have determined that it is complete, accurate and compatible with the source documents

Investigator's name Investigator's signature Date

Unique Identification No:

IDENTIFIERS- FOR CASES

Registration No:
Contact No:
Name:
Father's Name /Husband's Name:
Address:

DEMOGRAPHICS- CASES

Age:

Sex: Male ☐ Female ☐

Place of Residence: Urban ☐ Rural ☐

Social / Economical Status: a) Upper b) Upper Middle c) Lower Middle d) Upper Lower e) Lower

Education: a) Illiterate b) Primary c) Middle d) High School e) Intermediate f) Graduation g) Post-graduation & above

ANTHROPOMETRIC PARAMETERS- CASES

Height (mts) ☐

Weight (kgs) ☐

Body Mass Index (kg/ m^2) ☐

Unique Identification No:

INTEGRAL INSTITUTE OF MEDICAL SCIENCES AND RESEARCH

LUCKNOW -226026

SELECTION CRITERIA-- FOR CONTROLS

S. N.	**Criteria**	**YES**	**NO**
1.	Apparently healthy individuals		
2.	Subjects of age 40 and above		
3.	Individuals who have agreed to sign the consent form		

Subject is eligible for the study, if all **INCLUSION** criteria are **YES** and all **EXCLUSION** criteria are **NO**. **INVESTIGATOR STATEMENT**

I have verified the data entered in the control report form and have determined that it is complete, accurate and compatible with the source documents.

Investigator's name Investigator's signature

Unique Identification No:

IDENTIFIERS- FOR CONTROL

Registration No:

Contact No:

Name:

Father's Name /Husband's Name:

Address:

DEMOGRAPHICS- CONTROL

Age:

Sex: Male ☐ Female ☐

Place of Residence: Urban ☐ Rural ☐

Social / Economical Status: a) Upper b) Upper Middle c) Lower Middle
d) Upper Lower e) Lower

Education: a) Illiterate b) Primary c) Middle d) High School e) Intermediate
f) Graduation g) Post-graduation & above

ANTHROPOMETRIC PARAMETERS- CONTROL

Height (mts) ☐

Weight (kgs) ☐

Body Mass Index (kg/ m^2) ☐

ANNEXURE I (A)

INFORMED CONSENT FORM (FOR CASE)

1. I Poornima Dubey MSC 3rd year Medical Biochemistry, IIMS&R Lucknow.
2. For this study, I will take your 4 ml blood sample for the estimation of MDA and SOD.
3. The blood is only subjected for estimation of MDA and SOD and not for any other purpose.
4. There will be no charged /fees/any consideration will be given or taken for the study.
5. Your identity will be confidential and information and result of your blood test will not be revealed to any other except you if your desire.
6. This study has nothing to do with your treatment nor is it going to hamper the same if you refuse to participate.
7. The study nothing to do with your current treatment but may improve the knowledge and understanding of disease process and that knowledge may or not be helpful in future.
8. After knowing the all above detail would you like to participate in our study? Yes/No

CONSENT FORM (FOR CASE)

I……..…age.....W/OD/OS/O.....
.....R/O.....……. here with state that I have been duly informed about the study titled "**Comparative study of malondialdehyde and superoxide dismutase in Diagnosed cases of Benign Prostatic hyperplasia and control subjects** ", its prospects and consequences. I hereby give informed and written consent for the collection of my blood sample for the above said study only.

Signature/thumb impression of the patient:

Signature/thumb impression of the witness Signature of research scholar:

अनुबंध I (ए)

सूचित सहमति प्रपत्र (FOR CASE)

1. मैं पूर्णिमा दूबे रिसर्च स्कॉलर MSC 3rd मेडिकल बायोकेमिस्ट्री आईआईएमएसआर लखनऊ।
2. इस अध्ययन के लिए, मैलोनडिएलडिहाइड और सुपरआक्साइड डिसम्युटेजका के आकलन के लिए आपके 04 मिलीलीटर रक्त का नमूना लूंगी
3. रक्त केवल मैलोनडिएलडिहाइड और सुपरआक्साइड डिसम्युटेजका के आकलन के लिए है और किसी अन्य उद्देश्य के लिए नहीं।
4. अध्ययन के लिए कोई शुल्क नहीं लिया जाएगा / शुल्क / कोई विचार नहीं दिया जाएगा या लिया जाएगा।
5. आपकी पहचान गोपनीय होगी और यदि आप चाहें तो आपके रक्त परीक्षण की जानकारी और परिणाम आपके अलावा किसी अन्य को नहीं बताए जाएंगे।
6. इस अध्ययन का आपके उपचार से कोई लेना-देना नहीं है और न ही यह इसमें बाधा डालने वाला है यदि आप भाग लेने से इनकार करते हैं।
7. अध्ययन का आपके वर्तमान उपचार से कोई लेना-देना नहीं है, लेकिन रोग प्रक्रिया के ज्ञान और समझ में सुधार हो सकता है और यह ज्ञान भविष्य में मददगार हो भी सकता है और नहीं भी।
8. उपरोक्त सभी विवरण जानने के बाद क्या आप हमारे अध्ययन में भाग लेना चाहेंगे? हां /नहीं

सहमति पत्र (FOR CASE)

मैं……उम्र……डब्ल्यू/ओडी/ओएस/ओ…….....

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आर/ओ..... यहां यह बताने के साथ कि मुझे " बेनाइन प्रोस्टेट हाइपरपलेजिया में मैलोनडिएलडिहाइड और सुपरआक्साइड डिसम्युटेजका ", इसकी संभावनाओं और परिणामों के बारे में विधिवत सूचित किया गया है। मैं एतद्द्वारा उपरोक्त अध्ययन के लिए अपने रक्त के नमूने के संग्रह के लिए सूचित और लिखित सहमति देता हूं।

रोगी के हस्ताक्षर/अंगूठे का निशान

गवाह के हस्ताक्षर/अंगूठे का निशान शोधार्थी के हस्ताक्षर

ANNEXURE I (B)

INFORMED CONSENT FORM (FOR CONTROL)

1. I Poornima Dubey Research Scholar MSC 3rd Medical Biochemistry IIMS&R Lucknow.
2. I'm not associated with your treating doctor panel.
3. You are not suffering from benign prostate hyperplasia and you are not undergoing any such the treatment.
4. For this study, I will take your 4ml blood sample for the estimation of MDA and SOD.
5. The blood is only subjected for estimation of MDA and SOD not else for the study.
6. There will be no charged /fees/any consideration will be given or taken for the study.
7. Your identity will be confidential and information and result of your blood test will not be revealed to any other except you if u desire
8. The study not going to hamper if you refuse to participate.
9. The study will not be beneficial for you but may improve the knowledge and understanding of disease process and that knowledge may or not be helpful in future.
10. After knowing the all above detail would you like to participate in our study? Yes/No

CONSENT FORM (FOR CONTROL)

I……..…age.....W/OD/OS/O..... .....R/O.....……. here with state that I have been duly informed about the study titled **"Comparative study of malondialdehyde and superoxide dismutase in Diagnosed cases of Benign Prostatic hyperplasia and healthy control subjects",** its prospects and consequences. I hereby give informed and written consent for the collection of my blood sample for the above said study only.

Signature/thumb impression of the patient:

Signature/thumb impression of the witness Signature of research scholar

अनुबंध I (B)

सूचित सहमति प्रपत्र (FOR CONTROL)

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6. इस अध्ययन का आपके उपचार से कोई लेना-देना नहीं है और न ही यह इसमें बाधा डालने वाला है यदि आप भाग लेने से इनकार करते हैं।
7. अध्ययन का आपके वर्तमान उपचार से कोई लेना-देना नहीं है, लेकिन रोग प्रक्रिया के ज्ञान और समझ में सुधार हो सकता है और यह ज्ञान भविष्य में मददगार हो भी सकता है और नहीं भी।
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सहमति पत्र (FOR CONTROL)

मैं……उम्र……डब्ल्यू/ओडी/ओएस/ओ…….....
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रोगी के हस्ताक्षर/अंगूठे का निशान

गवाह के हस्ताक्षर/अंगूठे का निशान शोधार्थी के हस्ताक्षर

INSTITUTIONAL ETHICS COMMITTEE (IEC)

IIMS&R INTEGRAL UNIVERSITY, LUCKNOW

IEC/IIMS&R/2023/68

CERTIFICATE

This is to certify that research work entitled "**Comparative Study of Malondialdehyde and Superoxide Dismutase in Diagnosed Case of Benign Prostatic Hyperplasia and Control Subjects**" submitted by **Poornima Dubey, Dr. Saba Khan** for ethical approval before the Institutional Ethics Committee IIMS&R.

The above mentioned research work has been approved by Institutional Ethics Committee, IIMS&R with consensus in the meeting held on **30th December 2022**.

Dr.Q.S.Ahmed
(Member Secretary)
IRC/IEC
IIMS &R

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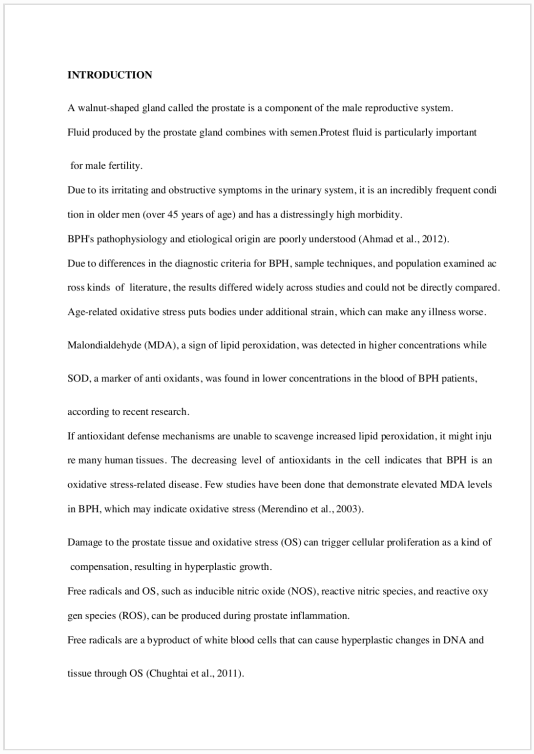

INTRODUCTION

A walnut-shaped gland called the prostate is a component of the male reproductive system.

Fluid produced by the prostate gland combines with semen.Protest fluid is particularly important for male fertility.

Due to its irritating and obstructive symptoms in the urinary system, it is an incredibly frequent condition in older men (over 45 years of age) and has a distressingly high morbidity.

BPH's pathophysiology and etiological origin are poorly understood (Ahmad et al., 2012).

Due to differences in the diagnostic criteria for BPH, sample techniques, and population examined across kinds of literature, the results differed widely across studies and could not be directly compared.

Age-related oxidative stress puts bodies under additional strain, which can make any illness worse.

Malondialdehyde (MDA), a sign of lipid peroxidation, was detected in higher concentrations while SOD, a marker of anti oxidants, was found in lower concentrations in the blood of BPH patients, according to recent research.

If antioxidant defense mechanisms are unable to scavenge increased lipid peroxidation, it might injure many human tissues. The decreasing level of antioxidants in the cell indicates that BPH is an oxidative stress-related disease. Few studies have been done that demonstrate elevated MDA levels in BPH, which may indicate oxidative stress (Merendino et al., 2003).

Damage to the prostate tissue and oxidative stress (OS) can trigger cellular proliferation as a kind of compensation, resulting in hyperplastic growth.

Free radicals and OS, such as inducible nitric oxide (NOS), reactive nitric species, and reactive oxygen species (ROS), can be produced during prostate inflammation.

Free radicals are a byproduct of white blood cells that can cause hyperplastic changes in DNA and tissue through OS (Chughtai et al., 2011).

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INTRODUCTION

A prostate is a component of the male reproductive system.Fluid produced by the prostate gland combines with semen.Protest fluid is particularly important for male fertility.

Due to its irritating and obstructive symptoms in the urinary system, it is an incredibly frequent condition in older men (over 45 years of age) and has a distressingly high morbidity.

BPH's pathophysiology and etiological origin are poorly understood (Ahmad et al., 2012).

Due to differences in the diagnostic criteria for BPH, sample techniques, and population examined across kinds of literature, the results differed widely across studies and could not be directly compared. Age-related oxidative stress puts bodies under additional strain, which can make any illness worse.

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NO, reactive nitric species, and ROS, can be produced during prostate inflammation.

Free radicals are a byproduct of WBC that can cause hyperplastic changes in DNA and

tissue through OS (Chughtai et al., 2011).

Vascular tissues, protein structures and activities, and genetic material can all be harmed by OS.

Additionally, it may lead to posttranslational changes, such as those necessary for apoptosis

and DNA repair (Sciarra et al., 2008).

In fact, oxidative stress (OS) can result in oxidative DNA damage, which can change the genome

in many ways such point mutations, deletions, or rearrangements.

Additionally, it may prevent DNA repair processes.

Furthermore, OS can modify the genetic changes in cellular DNA, upsetting the equilibrium between cell proliferation and cell death.

The research of Hamid et al. (2011), this interference with the regulation of planned cell death may result in hyperplastic or precancerous in alterations.

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The transcription element NF-B can be activated when it is exposed to OS by a combination of the TNF-/AP-1 transduction pathway and the NF-B-inducing kinase (NIK) transduction pathway.

NFkB, a master inflammatory transcriptional regulator, has as one of its target genes involved in NF-B activation by OS in the prostate can have a major impact on the start and

growth of prostate disorders (including inflammation and cancer). immune system inflammatory processes, cell proliferation, migration of cells, and apoptosis..

The local generation of cytokines that cause inflammation occurs inside the prostate epidermal cells as a consequence of direct stimulation of NF-B by proinflammatory soluble mediators (Wong et al., 2009).

In the healthy prostate gland, the NIK to the nuclear factor-B transduction pathway seems to be inactive. However, there is an increase in the TNF-/AP-1 transduction route in benign prostatic hyperplasia (BPH), which is followed by an increase in the apoptotic pathway, which helps to restrain excessive development of cells (Hamid et al., 2011).

A new connection between OS (oxidative stress) and imprinting loss was also discovered in a study. It proved, through increased NF-B activity, that OS promotes the loss of insulin-like growth component 2 imprinting in both cancerous and non-cancerous male cells of the prostate. Age-related imprinting loss is a major factor in the growth of tumours.In order to avoid age-related epigenomic changes, NF-B activity can be modulated (Yang et al., 2014).

A natural defence mechanism called the superoxide dismutase (SOD) enzyme system, along with vitamin C antioxidants such -as tocopherol and ascorbate, typically remove severely oxidative stressors. A reduction in the effectiveness of the antioxidant defence mechanisms may raise the severity of oxidative harm caused by ROS. The development of prostate tumours is also influenced by an imbalance between the MDA and SOD. (Khandrika et al., 2009).

The present study is designed to assess whole blood superoxide dismutase (SOD) activity and malondialdehyde (MDA) in benign prostate hyperplasia (BPH) and healthy subjects.

Review of literature

A prostate gland that enlarges is known as benign prostatic hyperplasia, the most common ailment in older men, especially those over 50. Before the fourth international BPH consultation, LUTS was referred to as "prostatism." LUTS can be highly inconvenient, disrupting daily activities and reducing quality of life. (Roehrborn et al., 1999). Men over the age of 40 are disproportionately impacted, and the disease's frequency rises with age to the point where 90% of men in their 80s are affected (McNeal et al., 1968).

An extremely common urological condition that mostly affects elderly men globally is BPH. Comprehensive information on its national, regional, and global burdens, as well as historical patterns, is lacking, though.

In comparison to 51.1 million cases (43.1 to 69.3) in 2000, the predicted global prevalence of BPH in 2019 was 94.0 million cases (95% UI 73.2 to 118).

There were roughly 2480 (1940 to 3090) cases of the disorder per 100,000 people, according to age-standardized prevalence data.

Between 2000 and 2019, the overall prevalence cases grew by 70.5% (from 68.6 to 72.7), w hereas the global age-standardized prevalence decreased by 7.70% (from 1.56 to 0.0912).

The average age-specific incidence of BPH varied from 6480 (5130 to 8080) cases per 100,000 people to 987 (732 to 1320) cases per 100,000 people in Eastern Europe, North Africa, and the Middle East in 2019.

Apoptosis, or programmed cell death, is a protective mechanism in the body that helps eliminate defective cells and prevent their accumulation and spread.

But both in vitro and in vivo, senescent cells do seem to be less prone to apoptosis brought on by oxidative stress (Muradian et al., 2001).

DNA and proteins can be altered by highly reactive aldehydes, such as 4-hydroxynonenal and MDA, which are byproducts of lipid peroxidation.

Events that are mutagenic, genotoxic, and cytotoxic may result from this.

Therefore, raised amounts of MDA and other reactive aldehydes could be the cause of DNA base changes in prostate cancer and BPH epithelium.

In a study, it was discovered that levels of MDA and PSA levels in BPH patients had a high correlation.

PSA is a helpful measure for identifying prostate cancer and figuring out whether recurrent tumours after radical prostatectomy have a malignant potential.

BPH patients also have higher PSA readings.

A measure of lipid peroxidation and inflammation in the prostate epithelium, higher circulating MDA levels may be useful, according to the substantial positive connection between MDA and PSA levels.

A patient with BPH may also have an increased chance of developing prostate cancer if their MDA levels are extremely high (Muradian et al., 2001).

In the development of BPH, various risk factors, beyond the direct hormonal effects of testosterone, play a significant role:-

Age:- Age is a significant factor influencing the prevalence of BPH. Age-related increases in the histopathological prevalence of BPH have been demonstrated in studies using corpses.

Numerous observational studies carried out in Europe, America, and Asia have shown that o

lder age is a risk factor for the start and clinical progression of BPH, as assessed by different metrics. (1997; Barry et al.).

Race: Regarding the relationship between race and the risk of BPH, there are no clear trends. Variable results have been found in observational studies comparing men of various races, including black, Asian, and white men. Black males tend to have larger prostate transition zones and total volumes than white men, according to studies carried out in the United States.

Lifestyle: It is becoming increasingly understood that certain lifestyle choices might affect how benign prostatic hyperplasia (BPH) develops and progresses.

Diet: Although the results are not uniform across all research, there is evidence that both macronutrients and micronutrients may have an effect on the likelihood of developing BPH. (Parsons et al., 2007)

Obesity: Studies repeatedly show a positive relationship between larger prostate volume and higher degrees of adiposity. This suggests that fat causes the prostate to enlarge. According to various research conducted in a variety of populations, a person's weight, an individual's body mass index , circumference of the waist, and volume of prostate are all closely associated with one another (Parsons et al., 2006).

Genetic Predisposition: A genetic tendency to benign prostatic hyperplasia (BPH) has been shown by cohort studies.According to one study, first degree relatives had a four-fold higher risk of developing BPH than the control group.

This shows that the onset of BPH may run in families (Lawrentschuk et al., 2021).

With greater frequencies of lower urinary tract symptoms (LUTS) identified, twin studies ha ve further validated these findings by establishing consistent results in the disease severity of BPH among monozygotic twins (Rohrmann, S., et al., 2016).

Pathophysiology

In men with BPH, static as well as dynamic variables may have a role in the development of lower urinary tract symptoms (LUTS) and obstruction of the bladder outlet (Caine et al., 198 6).

Prostate enlargement directly contributes to static blockage by compressing the perurethral area and obstructing the bladder exit.

In order to get past the resistance to urine flow caused by the compression, higher voiding pr essures are needed.

Further causing flow restriction is prostate enlargement's distortion of the bladder outflow (Foo, K. T. 2017).

A dynamic component of the prostate's smooth muscle tension. Alpha-blockers and 5-alpha reductase inhibitors are two medications that are used to relax smooth muscle and reduce prostate volume as a result.

The pathophysiology of BPH related symptoms is influenced by the tension in the smooth muscle (Lepor et al., 2005).

The prostatic urethra's flexibility and collagen content are decreased in males with BPH. By reducing compliance (flexibility) and raising resistance to urine flow, these alterations in collagen and elasticity may aggravate bladder outlet obstruction.

These changing variables may contribute to the explanation of why the size of the

prostate is not always an accurate indicator of the severity of BPH

(Babinski et al., 2014).

BPH diagnosis :

To ascertain if a man has BPH, a variety of important diagnostics tests and procedures are performed on men who exhibit symptoms of their lower urinary tract (LUT).examining the body in detail.

Physical examination

A complete physical examination should be performed, paying close attention to the

urinary system.

A healthcare professional should look for any signs of bladder distension in the suprapubic a rea. The penis should also be thoroughly examined for indications of phimosis, meatal

stenosis, or atypical penile lesions that may be related to lower urinary tract symptoms

(LUTS) (Gravas, S. 2015).

Urine analysis:

Urinalysis is a crucial diagnostic procedure that requires the collection of a urine sample for examination.

It aids in locating chemicals in the urine linked to renal failure, metabolic diseases, or urinar y tract infections.

The European Urological Association's recommendations state that even though there is littl e evidence to justify urinalysis, most professionals concur that its advantages outweigh its dr awbacks.

The initial examination of a patient presenting with lower urinary tract symptoms (LUTS) is

therefore advised to include a routine urinalysis, which can be carried out either dipstick ana lysis or microscopic evaluation (Chughtai, B., Forde, J. C., et al., 2016).

10

PSA(Prostate-specific antigen) test: -

The PSA test measures the PSA level, which has been shown to correlate with prostate volume (Cher, M. L., Abernathy, et al., 1996).

Renal Function: If there is a possibility that the kidneys are impaired, it is important to mea sure the blood creatinine levels or calculate the glomerular filtration rate (GFR).

For assessing kidney health, several diagnostic tests are essential (Gravas et al., 2015).

Imaging of the urinary system: Although routine upper tract imaging is not advised for pe ople with benign prostatic hyperplasia (BPH), there are several situations in which it may be required.

Patients who have a urinary tract infection, urolithiasis (urinary stones), renal failure, and/or hematuria (blood in the urine) are among those who fall into this category.

Urinary tract imaging becomes crucial in these situations for a thorough assessment (Chught ai et al., 201).

Oxidative stress

The phrase "oxidative stress" was first used by Helmut Sies1 to describe a lack of balance between the generation of oxidants and the antioxidants' protective effects, which could result in harm to biological systems (Sies, H., et al. 1985).

Redox signalling in physiological processes is now included in the area of redox biology, which has evolved over time from concentrating only on oxidative stress in

pathological circumstances.Our comprehension of the complex function redox signalling plays in diverse physiological circumstances has increased as a result of this evolution (Flohé et al., 2020; Sies et al., 2001).

Numerous studies have shown that oxidants contribute to the onset of a number of diseases, including cancer, chronic obstructive pulmonary disease (COPD), Alzheimer's disease, and atherosclerosis.These research have uncovered a wide range of methods through which oxidants cause cellular damage.

However, there are considerable differences in how much oxidative stress affects the pathophysiology of various diseases.

The effectiveness of boosting antioxidant defences may therefore be limited in some disorders since the underlying damage may not be sufficiently mitigated by just raising antioxidant levels (Pham-Huy et al., 2008).

Oxidative stress's functions in disease

Disease is influenced by oxidative stress in two main ways.

In the first pathway, oxidative stress leads to the production of reactive species such as hydroxyl radicals (•OH), peroxynitrite (ONOO), and hypochlorous acid (HOCl). Macromolecules such membrane lipids, structural proteins, enzymes, and nucleic acids are directly oxidised by these reactive species.

Cell malfunction and death result from the disruption of cellular function.

In the second pathway of oxidative stress, abnormal redox signalling is involved.

Under typical physiological circumstances, cells respond to stimulation by producing hydrogen peroxide (H2O2) as a second messenger.

The non-physiological overproduction of H2O2 under oxidative stress, however, can result in unregulated redox signalling, which breaks down cellular signalling pathways. The existence of both kinds of oxidative stress pathways inside a single disease and how they affect its pathophysiology should not be underestimated (Sies et al., 2017).

BPH and oxidative stress

BPH is thought to be influenced by a number of factors, including mediators of inflammation, hormones, dietary components, inflammatory genes, and oxidative stress (OS).

Among these, it is thought that oxidative stress and injury to the prostate tissue cause compensatory cellular proliferation, which in turn causes hyperplastic growth in the prostate. Free radical production inside the prostate may be stimulated by prostatic inflammation. Unsuccessful antioxidant defence mechanisms have the potential to worsen the level of Oxidative damage.

Prostate disorders emerge as a result of the delicate balance between oxidative stress (OS) and the antioxidant component. Multiple investigations have shown the involvement of oxidant products and the depletion of antioxidant molecules in BPH patients.

BPH is thought of as a condition that has the potential to progress into prostate cancer because free radicals are known to have a part in the carcinogenesis process. Notably, compared to people with BPH and healthy controls, prostate cancer patients had higher levels of OS markers and reduced antioxidant activity (Pac et al., 2010).

MDA, or malondialdehyde

Malondialdehyde is a byproduct of the body's lipid metabolism and is an organic molecule

Due to its high degree of reactivity, malondialdehyde is a member of the reactive electrophile species that induces cellular toxic stress and creates covalent protein adducts known as advanced lipid oxidation end products (ALE).

.Additionally, malondialdehyde can produce mutagenic DNA adducts when it interacts with

the DNA bases deoxyadenosine and deoxyguanosine.

It is important to note that malondialdehyde can be found in a variety of meals, but it is parti cularly common in foods that have gone bad (Merendino et al., 2003).

Antioxidant:-

Antioxidants are molecules that prevent oxidation, a chemical reaction that can produce free radicals and start a cascade of events that can damage organisms' cellular structures.

Thiols and ascorbic acid (vitamin C) are antioxidants that stop these chain reactions.

Both plants and animals have complex networks of overlapping antioxidants that work toget her to maintain a balanced oxidative state.

These include dietary antioxidants like vitamins C and E as well as naturally occurring antio xidants like glutathione and enzymes like catalase and superoxide dismutase (Pawar et al., 2 016).

SOD, or superoxide dismutase

All living things have a set of metalloenzymes called superoxide dismutase (SOD).

They are essential in the fight against reactive oxygen species' (ROS') damaging effects

(Kangralkar et al., 2010).

These enzymes play a key role in defending cells against harm brought on by elevated amounts of the superoxide anion free radical (O_2 -).

According to Yasui, K., and Baba (2006) (Mccord, et al., 1993), SODs effectively lower the concentration of O2 and prevent cellular damage by facilitating the dismutation of O2 into molecular oxygen and hydrogen peroxide (H_2O_2).

The metal ions in the SOD active site go through alternating reduction and oxidation reactions during this phase.

MDA and SOD level in BPH patients

Numerous mechanisms, including oxidative stress (OS), inflammatory mediators, hormonal factors, enzymatic factors, dietary factors, inflammatory genes, and the Gleason score gradin g system, which is used to determine the prognosis of prostate cancer (PCa), have been linke d to the development of prostate hyperplasia (Awodele et al. 2011).

Prostate hyperplasia is thought to be significantly influenced by oxidative stress (OS). It indicates a gap between the production of ROS (and the ability of cells to lessen the negative consequences of those organisms, as stated by Jones et al. (2007). Prostate hyperplasia is also influenced by genes and inflammatory mediators, which exacerb ates oxidative stress (El Gaafary, M., et al 2015).

Through modifications to intracellular glutathione levels and the activity of detoxifying enzy mes like gamma

glutamyl trans peptidase, hormones, especially androgens, can affect the levels of

Oxidativestress.The cellular prooxidant-antioxidant equilibrium can be upset by changes in

hormone levels, which increases oxidative stress (Shankar et al., 2015).

Additionally, the development of prostate hyperplasia has been linked to enzymatic variable s, nutritional factors, and the Gleason score grading system, a PCa prognosis tool

(Almushatat et al., 2006).

The by products of typical cellular metabolism, reactive nitrogen species (RNS) and

reactive oxygenspecies (ROS), have an effect on cell signalling.

Oxidative stress can be brought on by high amounts of ROS and RNS, which causes cells to activate a number of defence mechanisms to deal with the alterations (Li et al., 2014).

Although numerous studies have been done on this subject, it is still unknown how oxidative

The fact that these pathways do not coexist and that a combination of these factors probably affects prostate hyperplasia is significant (Gaafary et al., 2015).

Particularly few research have examined the function of MDA and SOD in BPH patients.

The goal of this study is to determine whether malondialdehyde (MDA) and superoxide

Dismutase (SOD) is related to the onset and severity of BPH.

AIM:-

The Purpose of the study is to find relationship between malondialdehyde (MDA) Superoxide dismutase (SOD) in diagnosed cases of BPH and control subjects.

OBJECTIVES:-

1. To determine the level of malondialdehyde (MDA) in diagnosed cases of BPH patients and control subjects.
2. To determine the activity of Superoxide dismutase (SOD) in diagnosed cases of BPH patients and control subjects.

To study to determine the correlation of malondialdehyde and superoxide dismutase in diagnosed cases of benign prostate hyperplasia patients and control subjects.

Observations and results

Age and BMI in BPH -

In this study, 30 control Subjects aged 40 years and above along with 30 benign prostate hyperplasia (BPH) patients were included. The mean age of control subjects (50.56 ±3.67) and BPH patients (50.16 ±6.29) have been found not statistically significant, And the mean of BMI control subjects (27.43 ±3.54) and BPH patients (27.53 ±3.72) have been found not statistically significant (Table. 1)

Table: 1 Age and BMI wise distribution of cases and control.

Parameters	N	Controls (Mean / ±SD)	Cases (Mean / ±SD)	p-value	Significance
Age (Years)	30	50.56 ±3.67	50.16 ±6.29	0.8536	Not statistically significant
BMI (kg/m^2)	30	27.43 ±3.54	27.53 ±3.72	0.915	Not statistically significant

N= Number of control or cases when p<0.05 significant

MDA and SOD -

Results showed that mean of MDA was found significantly elevated in cases as compared to controls ($p<0.001$). However, mean of SOD was found significantly reduced in cases as compared to controls ($p<0.001$), shown in (Table 2.)

Table: 2 Mean and standard deviation of the MDA and SOD in cases and controls.

MDA and SOD (µmol/L)				
Variables	**Controls Mean ±SD (N=30)**	**Cases Mean ±SD (N=30)**	**p-value**	**Significance**
MDA (µmol/L)	1.24±0.29	3.06±0.32	**<0.001***	Statistically significant
SOD (U/mg of protein/min)	6.98±0.86	0.87±0.30	**<0.001***	Statistically significant
**. Correlation is significant at the 0.05 level (2-tailed).* *Data represented as Mean* ±SD				

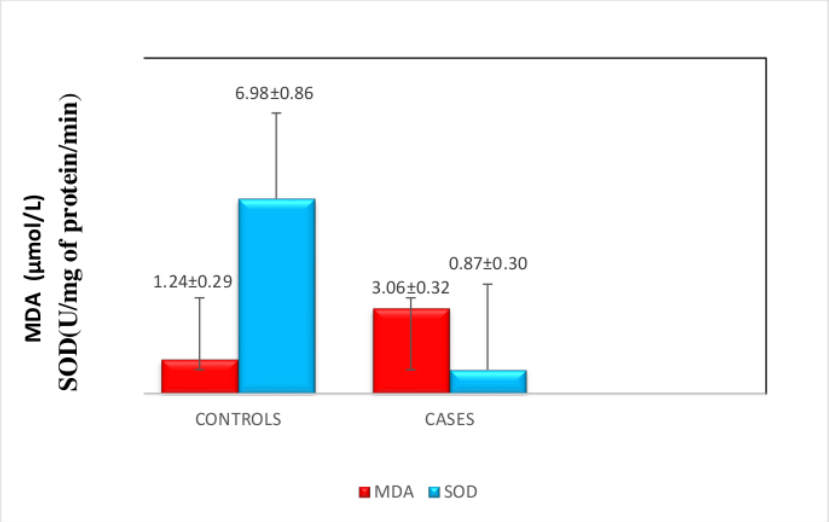

Figure: Comparison of MDA and SOD in cases and controls.

Karl Pearson's correlation coefficient among the study parameters in cases

Results showed that MDA has a significant negative correlation with SOD among cases ($r = -0.431$, $p<0.05$), shown in (Table: 3)

Table 3: Pearson Correlations Analysis among Cases

Variables		SOD (U/mg of protein/min)
MDA (µmol/L)	Pearson Correlation	**-0.431***
	Sig. (2-tailed)	.017

	N	30

*. *Correlation is significant when p value less than 0.05 level.*

N= Number of cases

MDA: Malondialdehyde, SOD: Superoxide dismutase

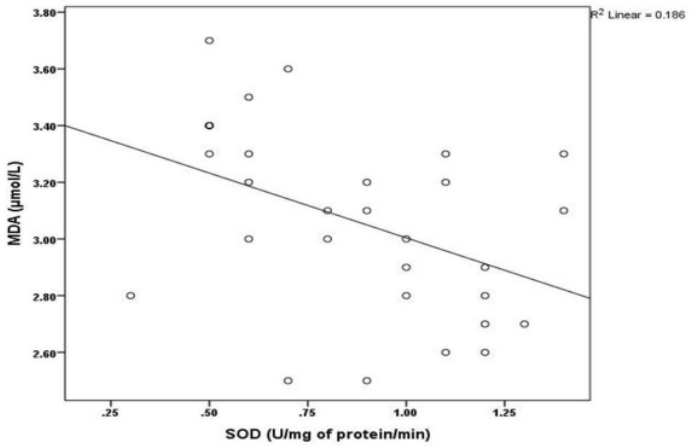

Figure- Scatter diagram showing correlation between MDA and SOD.

Discussion

Excessive production of free radicals can cause direct damage to various biological molecules such as DNA, proteins, lipids, and carbohydrates through a process called oxidation. In this study we observed that the malondialdehyde concentration was significantly increased in BPH individuals (3.06±0.32) compared to Controls (1.24±0.29) (μmol/L) .

The results are consistent with (Margaritis, I., et al., 2003), who observed that BPH patients have higher MDA concentrations than control group members, and this difference was show n to be statistically significant.

When free radicals interact with these biological molecules, they can result in oxidatie dama ge since they are extremely reactive molecules with unpaired electrons.

One of the secondary effects of excessive free radical production is the generation of metaboslites during lipid oxidation, a process known as lipid peroxidation. Lipid peroxidation leads to the formation of various products, including aldehydes, with one of the most studied and commonly measured aldehydes being malondialdehyde (Margaritis, I., et al., 2003).

Due to its high cytotoxicity and inhibition of antioxidant enzymes, MDA is particularly note worthy. The term "cytotoxicity" describes a substance's capacity to harm or kill cells, and

MDA has been demonstrated to possess such abilities.. Additionally, MDA can interfere with the activity of antioxidant enzymes, which are responsible for neutralizing free radicals and protecting cells from oxidative damage. By inhibiting antioxidant enzymes, MDA assist in the build-up of free radicals and oxidative stress. The combined effects of the cytotoxicity of MDA and its inhibitory action on antioxidant enzymes make it capable of

acting as a cancer promoter and a carcinogenic agent. Cancer promotion refers to the stimulation or enhancement of the growth and development of cancer cells, while carcinogenic agents are substances that, in combination with a carcinogen, increase the likelihood of developing cancer (Sheeja et al ., 2006).

In our study of blood samples from patients with BPH, we observed a significant reduce in the enzymatic activity of cytosolic SOD in cases (8.47±1.33) as compared to controls (6.98±0.86) (U/mg of protein/min) respectively. This decline in SOD activity can be attributed to the response of the body to moderate levels of superoxide anions present in these cells, which involves the up regulation of SOD (Pincemail et al., 2002). Research conducted by Jung et al. (1997) has shown that the decrease in SOD enzymatic activity increase in the accumulation of mutated DNA bases is linked to BPH.

This is accomplished by lowering the harmful effects of the superoxide radical (O_2) and other radicals produced by subsequent processes by catalysing The superoxide dismutase (SOD) enzyme is a crucial part of the antioxidant defence system because it directly eliminates reactive oxygen species (ROS). their dismutation into hydrogen peroxide (H_2O_2) (Pasupathi et al., 2009).

The study also showed a correlation between MDA concentration and Age, further solidifying the fact that in the age-related BPH, OS plays a crucial role in disease progression. According to our data, though the research project was conducted in case and control patients of the same age group 50.16±6.29 for cases and 50.56±3.67 for control, there was a significant change in OS levels. The data further suggests that Age is not a factor in the antioxidant functioning. Antioxidant role and efficiency is not dependent on age but

rather dependent on the OS levels exerted on a body. Oxidative stress significantly affects antioxidant performance.

SUMMMARY

The goal of the current study was to evaluate the MDA and SOD levels in BPH patients with a diagnosis and healthy controls.

Estimated parameters were:

- Malondialdehyde (MDA)
- Superoxide Dismutase (SOD)

The levels of the aforementioned parameters were compared between the cases and control groups.

The observation made in the study was as follows:

- The control group's average age was 50.56±3.67 years, but the patients' average age was 50.16±6.29 years.

  The mean ages between the groups did not differ significantly (0.8536).

- The mean MDA levels for the control group were 1.24± 0.29 while they were 3.06± 0.32 (μmol/L) for the patients.Between the groups, there was a significant difference in mean MDA levels (< 0.001).

- There was a significant difference in the mean SOD activity between the groups (< 0.001): the mean SOD activity of the control group was 6.98±0.86, whereas the mean SOD activity of the cases was 0.87±0.30(U/mg of protein/min).

CONCLUSIONS

This study provides evidence that the development of BPH is accompanied by an impaired oxidative status, which manifests as elevated levels of malondialdehyde (MDA), depletion of antioxidant activity, and decreased enzymatic activities of superoxide dismutase (SOD).

Overall, this study sheds light on the importance of investigating oxidative status and its impact on cellular processes in BPH, providing valuable insights for further research and the development of novel therapeutic strategies.

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