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# HORMONAL DISTURBANCES IN PATIENTS WITH BENIGN PROSTATE HYPERPLASIA

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## Abstract

Benign prostatic hyperplasia (BPH, benign prostatic hypertrophy), a non-malignant abnormal growth of the prostate gland, affects almost all men in some degree as they age and can cause a significant disruption of lifestyle due to urinary outflow obstructive and irritative symptoms.

The present study was performed on patients with BPH and other group of normal persons (40 person for each) to evaluate some of hormonal changes that result in BPH. The blood samples were collected from the groups of study those were of ages 45 and more and serum levels of both estrogen and testosterone were evaluated, as well as tissue of prostate were collected from some of the patients after surgery and estrogen receptors were estimated by immunohistochemisitry.

The results shows significant reduction of the testosterone with elevation of the estradiol levels with marked expression of estrogen receptors in both epithelial and stromal cells of the prostate in patients.

In conclusion, the present study found that sex hormonal disturbances associated with increase age of the person was implicated in the pathogenesis of BPH.

## Introduction

Benign prostatic hyperplasia (also known as benign prostatic hypertrophy or BPH) is one of the most common conditions in middle-aged and elderly males, with an incidence of approximately 50-60% in males aged 40-60, and greater than 90% in men over 80.

Benign prostatic hypertrophy is characterized by a non-malignant hypertrophy of the prostate which is caused by hormonal processes and/or imbalances within the glandular tissue[1].

Hyperplasia begins in the periurethral region and includes the stromal, epithelial, and smooth muscle tissues of the gland. The fibrous capsule surrounding the gland forces most of the growth inward, compressing the urethra and causing the typical urinary symptoms characteristic of this disease.

Despite the high impact of BPH on public health, however, the pathogenesis of BPH is still largely unresolved. Indeed, although multiple theories have been proposed, the aetiology of BPH still remains uncertain in some aspects. Several mechanisms seem to be involved in the development and progression of BPH. Although ageing represents the central mechanism implicated, recent novel findings also highlighted the key role of hormonal alterations, metabolic syndrome, and inflammation[2].

Previous causal models have focused primarily on sex steroid hormones, which are essential to normal prostate growth and development[3] it is probably linked to age-related changes in hormonal and other growth-regulatory factors that affect prostate growth[4]. Testosterone and estrogens play important roles in prostate growth and function, and many scientists have hypothesized that the slow decline in serum testosterone levels or the

decreasing ratio of testosterone to estrogen that begins in midlife are factors in BPH pathogenesis[2].

It is now well accepted that serum testosterone (T) levels decline progressively with aging in men[5,6]. This decline is associated with alterations in body composition; diminished energy, muscle strength, and physical function; reduced sexual function; depressed mood[4].

Estrogens play key roles in the development and maintenance of reproductive function and fertility[7,8]. Estrogens also have an important role in pathological processes observed in tissues of the reproductive system[9]. In addition, they exert a vast range of biological effects in the cardiovascular, musculoskeletal, immune, and central nervous systems[10]. The most potent estrogen produced in the body is 17β-estradiol (E2). Although estrone and estriol, two E2 metabolites, bind to estrogen receptors (ESRs) with high-affinity,they are much weaker agonists compared to E2[11].Whereas serum estrogen levels are low in healthy men [approximately half the levels in nonpregnant women[12]], serum and intraprostatic estradiol levels (both absolute levels and those relative to testosterone) increase in men with age, accompanied by an increase in the prostate volume[13,14]. In addition, patients with larger volumes of BPH tend to have high levels of serum estradiol[15]. Therefore, the estrogen-dominant status in men after middle age has been implicated in the induction and progression of BPH[16]. However, the molecular mechanism of estrogen action in the development of human BPH is largely unknown. Estrogens require the presence of estrogen receptors (ERs) for their actions. ERs belong to a nuclear receptor superfamily of ligand-activated transcription factors; and, at present, two types of ERs (ERα and ERβ) have been characterized[17]. ERα was known as ER before the discovery of ERβ, and its distribution has been thoroughly investigated in various human organs, including prostate and endometrium, breast cancer cells, and ovarian interstitial cells, which contain mostly ERα[15,13]. ERβ has been detected in stromal cells of human prostate, although the cellular localization of ERα remains controversial[18]. ERβ has been recently cloned in the rat prostate and humantestis[19,20].

## Patients and methods

Patients: groups of study were two, (40 person with different ages for each group) the patients in the first group were with history of benign prostate hyperplasia which were diagnosed depend on the clinical signs and the sonography which were done in Al-sader Hospital Missan–Iraq and histopathology of the prostate gland, and the persons in the second group which is the control group have no history of BPH.

Hormonal measurement: blood samples were collected from individuals of both groups and the serum level of testosterone and estrogen hormones had been estimated by Minividus.

Histopathological examination: tissue of prostate were obtained from 10 patients after partial or complete prostatectomy, the tissue were fixed directly by 10% formalin then processed and sectioned to 5µm, the sections stained with routine stain (hematoxylin and Eosin) to confirm the hyperplasia, others stained with immunohistochemichal stain specific for estrogen receptors (ERα & ERβ) to reveal the expression and the distribution of these two receptors in the prostate tissue.

Statistical analysis: the statistics was accomplished by the SPSS version 16 with application by axel, confidence level 0.99 (α – 0.01).

## Results

All patients with (BPH) showed marked disturbances in the level of both estradiol and testosterone in comparison with the

data of the normal persons (tables I & II) whom exhibit accepted ranges in the level of both estradiol and testosterone hormones.

## Discussion

Our results shows that the estradiol level was within normal ranges (20–60 pg/ml) in the control group while there were marked elevation in the levels of estradiol in the patients with (BPH) in which the levels appears either in the upper normal or higher than the normal level, this increase was related to the age in which correlation was highly significant at ($P \leq 0.01$) where the estradiol level begin to increase in the age of 50 years in men, this result was agreed with reference[21],This rise is exacerbated by stress, disease, malnutrition, and hypothyroidism (which are also associated with old age). Estrogen is produced in fat[22] and fat tends to increase with age, especially when thyroid and progesterone are deficient[23]. The correlation between the level of the estradiol and the age in the patients of study revealed in the diagram (I).

The prostate tissue which collected from the patients reveal hyperplasia as most commonly observed in the transitional and periurethral zone as depicted in the (figure 1&2) this result in consistent with reference[8].

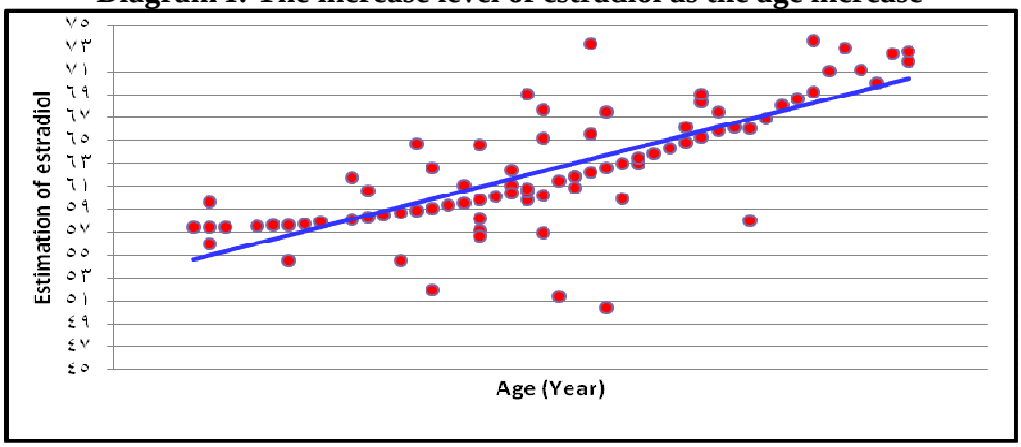
The results of immunohistochemical stain for the same regions of the prostate reveal that estradiol appear to exert its influence on the prostatic tissue through the estrogen receptors expressed by the cells in the prostate this results come in line with the result of other researchers who report that Circulating levels of free estradiol remain constant in the ageing man due to an age-related increase in body weight and adipose cells. Indeed, the prevalence of fat tissue is responsible for the expression of high levels of aromatase, which produces estrogen conversion[24], and this result attributed to the increased estrogenic stimulation of the prostate in the ageing man may lead to the reactivation of prostatic growth[25,26]. Estrogen-induced aberrations in prostate epithelial growth have also been observed in dogs, monkeys, and humans[27,28]. In addition to epithelial effects, estrogens also stimulate stromal cell proliferation[29,5]. Indeed, in vitro studies suggest that up regulation of estrogen receptor a in cultured prostate stromal cells is also associated with regulation of fibroblast growth factor (FGF)-2 as well as other growth factors. Moreover, several studies demonstrated that the addition of androgens down regulated the estrogen receptor and various stroma-derived growth factors[12,21]. Finally, estrogen effects on the prostate gland may also be indirectly mediated through alterations in other serum hormones[18,25].

Immunohistochemical stain specific for these receptors shows the distribution of the these two receptors in the prostatic tissue, in which the estrogen receptor (ERα) appear to be distributed mostly in the stromal tissue (figure 3) this result inconsistent with reference[10] while the estrogen receptor (ERβ) distributed in the epithelial cells of the prostatic glands and in the stromal cells (figure 4) this result come in line with the results of reference[7].

The result show that the level of testosterone were within normal range (normal=3-10 ng/ml) in the person of control group, while there were marked suppression in the level of the testosterone in the patients with benign prostate hyperplasia in which the levels was either in the lower normal or subnormal, the correlation between testosterone level and the age was significant at ($P \leq 0.01$), diagram (II), this result was agreed with result of other researcher[26-32]. Moreover, anti-androgen treatments have a limited or transient effect on BPH; while the circulating androgen in the serum reduces to castrated levels, intraprostatic androgen and dihydrotestosterone (DHT) levels remain persistently high and the activities of androgen receptors (AR) remain elevated[33-39]. Testosterone, in its free form

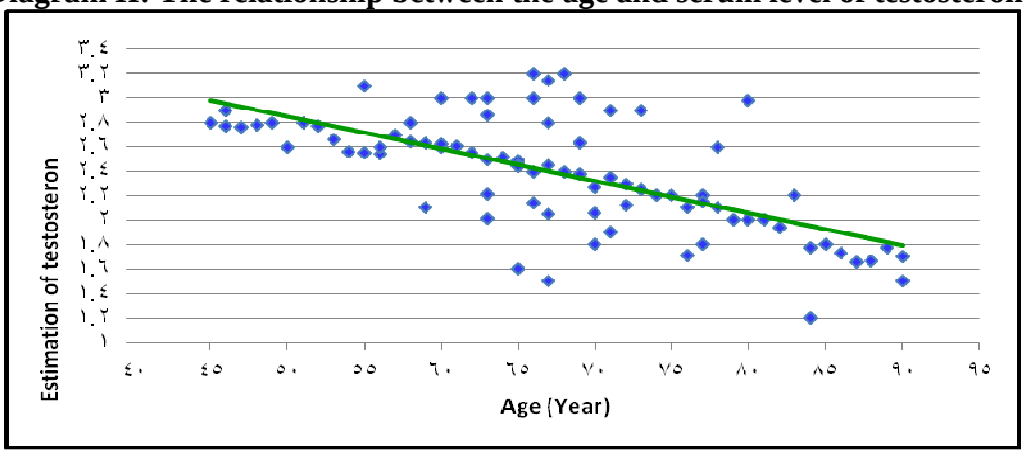
(unbound to proteins) diffuses into prostate cells and is known to be the promoter of prostate cell proliferation[10]. It is mainly produced by the testes, and under normal conditions, reaches the systemic blood through the testicular venous drainage system. It eventually reaches the prostate via the prostate artery after it has passed through the venous and arterial circulation, where it undergoes marked dilution and more than 98% of it binds to albumin and sex-hormone-binding globulin (SHBG) in which form it is not able to diffuse into the prostatic cells. Upon entering the prostatic cell cytoplasm, 90% of the FT is converted irreversibly by the 5a-reductase enzymes, to DHT - a more potent hormone- which has an obligatory role in the development of BPH. DHT has a more than five folds higher affinity for AR than does FT[39-42]. The idea of the this research also support that the administration of the exogenous testosterone also exert the same effect on the prostatic tissue because the free level of testosterone in the plasma is controlled by the pineal gland, this gland will measures a notable rise in testosterone so it sends a chemical signal to the pituitary gland which in turn releases a hormone into blood stream which converts allot of the testosterone into estrogen. The presence of estrogen in blood stream causes the testicles to cut way back on production of both testosterone and semen. The result is less testosterone than ever and if keep introducing it into veins from an external source, this will result in disturbance in the levels of both testosterone and estradiol in the blood[25].

**Diagram I: The increase level of estradiol as the age increase**




Mean the level of estradiol in the given age.

**Diagram II: The relationship between the age and serum level of testosterone**




Mean the testosterone level in the given age

**Table I: The descriptive statistical analysis of the data of normal group**

| | N | Minimum | Maximum | Mean | S. D |
|---|---|---|---|---|---|
| Age | 40 | 53.00 | 73.00 | 63.3500 | 5.13185 |
| Esradiol | 40 | 20.65 | 55.20 | 37.9705 | 1.34368 |
| Testosterone | 40 | 3.50 | 9.98 | 7.3410 | 1.85519 |

**Table II: The descriptive statistical analysis of the data of BPH patients**

| | N | Minimum | Maximum | Mean | S. D |
|---|---|---|---|---|---|
| Age | 40 | 46.00 | 90.00 | 66.5641 | 9.24461 |
| Estradiol | 40 | 50.43 | 73.70 | 61.9151 | 5.77725 |
| Testosterone | 40 | 1.05 | 3.20 | 2.4408 | 0.60180 |

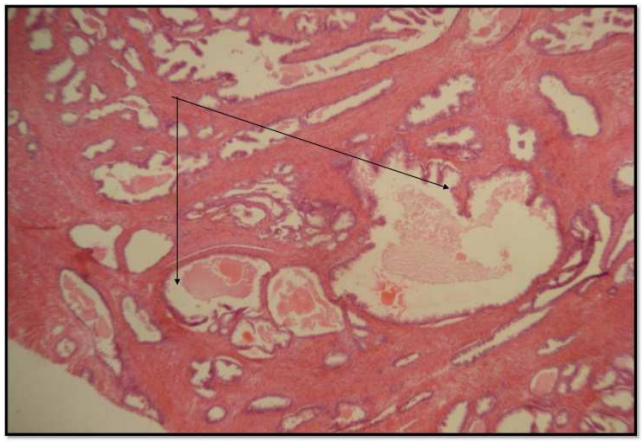


**Fig. 1: Section of prostate tissue reveal the cystic dilatation of the gland with multiple projections (H&E) (500X)**

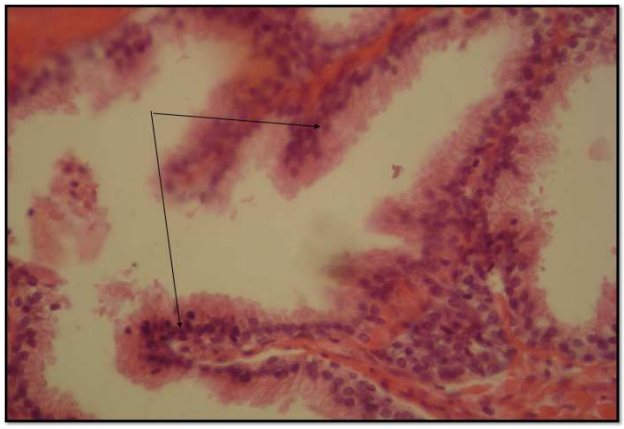


**Fig. 2: Section of prostate tissue reveal multiple projections with multiple layers of cells (H&E) (500X)**

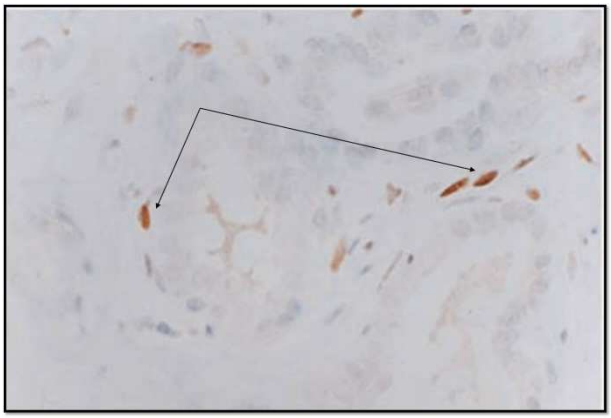


**Fig.3: Immunohistochemical stain of estrogen receptor (ERα) reveal the expression of this receptor in the stromal cells of the prostate (500X)**

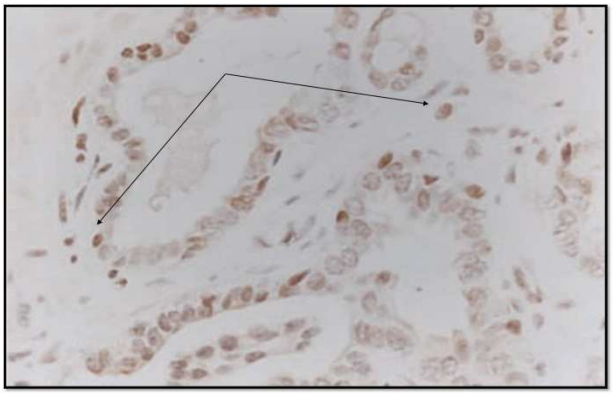


**Fig.4: Immunohistochemical stain of estrogen receptor (ERβ) reveal the expression of this receptor in both epithelial and stromal cells of the prostate (500X)**

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