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Endocrine control of benign prostatic hyperplasia

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SUMMARY

Benign prostatic hyperplasia (BPH) is the most common benign proliferative disease among aging men. Androgens play a key role in the development and growth of the male genital tract favoring differentiation and proliferation of stromal and epithelial cells of the prostate gland. It is known that growth factors play a crucial role in the cross-talk between stromal cells and epithelial cells. These factors, mainly secreted by stromal cells, act in an autocrine/paracrine manner to maintain prostate cellular homeostasis. A number of experimental studies support the interdependence between growth factors (IGF, FGF, TGF) and the steroid hormone milieu of the prostate. Alterations of these interactions may alter the balance between proliferation and cell death leading to the development of BPH. The onset of BPH is closely related to an inflammatory microenvironment. Chronic inflammation, which generally follows the acute inflammation because of infectious agents, is favored by hormonal or metabolic abnormalities. However, a close correlation between these mechanisms and metabolic or sexual hormones (androgen/estrogen ratio) alteration has been shown suggesting a key role of hypogonadism in the development of prostate inflammation. This review clear shows that the BPH pathogenesis and the subsequent onset of the lower urinary tract symptoms (LUTS) depends from different etio-pathogenetic factors whose mechanism of action remains to be evaluated.

INTRODUCTION

The most common benign proliferative disease among men during aging is benign prostatic hyperplasia (BPH). Its incidence increases by 42% in men between 40 and 50 years up to 90% in those over 80 years (McVary, 2006). BPH is a hyperplastic process of the prostate that develops in the transition zone (TZ), particularly in the periurethral area, and is characterized by hyperplasia of the stromal component, and to a lesser extent, of the epithelial cells (McNeal, 1990).

Benign prostatic hyperplasia is clinically characterized by an increase prostate volume (benign enlargement of the prostate, BEP), detectable by ultrasound or digital rectal examination which causes cervical-urethral obstruction because of the mechanical compression exerted on the urethra (benign prostatic obstruction, BPO).

Benign prostatic hyperplasia is therefore a disease that occurs during aging characterized by the development of a broad spectrum of symptoms associated with the functions of the lower urinary tract (low urinary tract symptoms, LUTS) (Roehrborn, 2008; Nicholson & Ricke, 2011; Vignozzi *et al.*, 2014). These symptoms depend on two components: the static one which is caused by the mass of the gland, and the dynamic one, because of the tone of the smooth muscle of the bladder neck, prostate and its capsule. α1-adrenergic receptors play a crucial role in these mechanisms.

Low urinary tract symptoms may be categorized into two types: filling or irritative symptoms (increased frequency of urination, nocturia, urinary urgency, burning during urination) and voiding or obstructive symptoms (reduced urinary flow and incomplete emptying of the bladder) (Abrams *et al.*, 2009). The changes caused by BPO into the bladder can also be divided into two phases: an initial one characterized by an obstruction compensated by an increased detrusor muscle activity (detrusor instability) subsequently to the incomplete emptying of the bladder; and a second phase characterized by a reduced activity of the detrusor contractility. It is noteworthy that LUTS are also associated with other abnormalities such as inflammation and α-adrenergic receptor (α1) hyperactivity on the prostate gland and the muscle components of the bladder (Donnell, 2011; Vignozzi *et al.*, 2012).

Androgens play a crucial role in the differentiation and into prostate growth during the fetal period and puberty, whereas they play a permissive role during adulthood (Ho & Habib, 2011). The role of androgens in the development of BPH is still

controversial. Although the α-blockers are frequently prescribed for BPH treatment, they are not able to reduce the volume of the gland and are often insufficient to eliminate the symptoms of the prostatic disease. Conversely, 5α-reductase inhibitors (5-ARI), which suppress the conversion of testosterone (T) into its active metabolite dihydrotestosterone (DHT), are particularly effective in reducing the volume of BPH (Barkin, 2011). Clinical data indicate that the association between 5-ARI and α-blockers produces a better clinical improvement compared with each molecule administered alone. This suggests that the interaction between androgen/androgen receptor (AR) plays a crucial role in the development of BPH (reawakening theory); hence changing the activity of this pathway can represent the best therapeutic approach. On the other hand, the incidence of BPH increases with aging and with the related reduction in testicular T production (Harman *et al.*, 2001). Therefore, it may be hypothesized that other factors such as growth factors, estrogen, inflammation, may play a key role in BPH etiology.

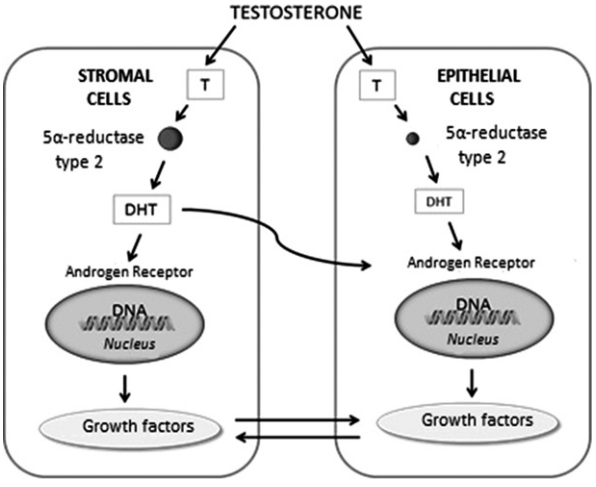
BENIGN PROSTATE HYPERPLASIA: ROLE OF THE ANDROGEN PATHWAY

Signaling pathway androgen/androgen receptor

Androgens play a key role in the development and growth of the male genital tract favoring differentiation and proliferation of stromal and epithelial cells of the prostate gland. In the prostate, the enzyme 5α-reductase type 2, more expressed in stromal cells, converts T into DHT, the main androgen in this tissue (Fig. 1).

5α-reductase is an enzyme responsible for the conversion of T to DHT. The latter is the more potent androgen and its activity is 4–5 times higher than that of T, 5α-reductase makes simple the double bond existing between carbon 4 and carbon 5. This modification greatly increases the affinity of DHT to androgen receptors, enhancing, consequently, the activity. 5α-reductase is expressed especially in the prostate, testes, hair follicles, and adrenal glands. Its action is important already during the uterine life, when DHT determines the development of the male external genitalia. In the cases of recessive genetic defect isoform 5α-reductase type II is insufficient, there is an abnormal development of the external genitalia in the fetus, which results in disorders of sexual and infertility in adulthood. From puberty onwards, DHT supports the development of the secondary sexual characteristics, such as the lowering of the voice, growth of facial hair and body, the receding hairline, and sebum secretion. DHT is also important for the development of muscle mass and, psychologically, for the appearance of the sexual behavior. An excess is involved in the development of BPH, acne, seborrhea, androgenetic alopecia, and hirsutism. A deficit of DHT is implicated in the occurrence of gynecomastia (Bartsch *et al.*, 2000; Azzouni & Mohler, 2012). In the human body there are two isoforms of the 5α-reductase, encoded by two different chromosomes and with different sensitivity to regulatory factors, respectively, called 5α-reductase type I and 5α-reductase type II. The isoform of type I is mainly concentrated in the skin, sebaceous glands, central nervous system, and liver. The type II isoform is expressed primarily in the prostate and at the level of the hair follicles. To inhibit the activity of these enzymes they have been developed two drugs. The first, called Finasteride, is a selective inhibitor of type II isoform. The second, called Dutasteride inhibits both isoforms (Bartsch *et al.*, 2000; Azzouni & Mohler, 2012).

Figure 1 In the stromal cell a majority of testosterone (T) is converted to dihydrotestosterone (DHT) by enzyme 5α-reductase type 2. DHT acts stimulating the proliferation of stromal and epithelial cells with autocrine and paracrine signaling. Such action may be direct or mediated by the production/activity of several growth factors.



Approximately 90% of prostatic androgens are in the form of DHT, derived mainly from testicular androgens (only 10% comes from androgens of adrenal origin). DHT acts in an autocrine manner into the stromal cell or in a paracrine manner on the nearby epithelial cells. In prostatic cells, DHT binds with high affinity to the androgen receptor (AR) (Roehrborn, 2008; Nicholson & Ricke, 2011; Vignozzi *et al.*, 2014)., which translocates into the nucleus to bind to specific androgen responsive elements in the promoter region of target genes stimulating the transcription and ultimately protein synthesis. The inactivation of key androgen-dependent genes (e.g., prostate-specific antigen) and androgen deprivation leads to the activation of specific genes involved in programmed cell death. In addition to these direct effects, DHT acts also by regulating the expression/activity of several growth factors and their receptors, such as epidermal growth factor (EGF), insulin-like growth factor 1 (IGF-I), and fibroblast growth factor (FGF)-related proteins such as keratinocyte growth factor (KGF) (Carson & Rittmaster, 2003) (Fig. 1).

In humans, prostate development and growth occur in three distinct phases. The first phase occurs during the fetal period and ends at birth; the second one begins at puberty, with a process of cell development and differentiation leading to the adult prostate; and the third one of selectively volumetric growth develops in adulthood and during aging and involves only one of the three different anatomical areas of the prostate, the periurethral zone or TZ, leading to the development of BPH. Although the development of the prostate during the first two phases is clearly an androgen-dependent process (Corona *et al.*, 2011), the role of androgens on the development of BPH is still debated. The incidence of BPH increases continuously during aging concomitantly with a decreased testicular function and, therefore, in presence of lower serum T levels (Harman *et al.*, 2001; Lenzi *et al.*, 2009). Moreover, no correlation between serum T levels and prostate size has been found clinically (Roehrborn, 2008; Nicholson & Ricke, 2011; Vignozzi *et al.*, 2014). Finally, treatment with androgens in hypogonadal

patients does not appear to increase the risk of development of BPH/LUTS and, in some cases, androgen replacement therapy appears to be correlated with an improvement of LUTS (Shigehara *et al.*, 2011; Corona *et al.*, 2014; Vignozzi *et al.*, 2014). These observations seem to support, therefore, the hypothesis that androgens are not directly related to the development of this disease.

On the other hand, several experimental and clinical studies have shown different results. Indeed, T replacement therapy in young castrate dogs causes BPH development. Clinical studies showed that BPH never develops in men undergoing surgical castration before puberty, as well as in patients with primary or central hypogonadism (Nicholson & Ricke, 2011). Men with a reduced expression of the enzyme 5α-reductase type 2 have a small prostate (Imperato-McGinley & Zhu, 2002); furthermore, in men with congenital deficiency of 5α-reductase type 2 do not have palpable prostate and the presence of a normal prostate epithelium is rare (Imperato-McGinley & Zhu, 2002).

More recently, the role of the AR as a promoter of the development of prostate tissue has been shown by the suppression of AR in transgenic mice that spontaneously develop BPH as a result of prolactin (PRL) overexpression. These studies demonstrate that the signaling pathway of PRL is important for stromal cell proliferation and that the AR receptor is able to modulate the epithelium-stromal cell interaction (Lai *et al.*, 2013). Finally, it noteworthy that 5-ARI (dutasteride, finasteride) administration is able to significantly decrease the size of the gland and, for this reason, 5-ARI is the treatment of choice in patients with BPH (Barkin, 2011).

To explain these conflicting observations, it has been hypothesized that DHT intraprostatic concentrations, rather than circulating T levels, are implicated in the development of prostatic hyperplasia (Vignozzi *et al.*, 2014). Indeed, both AR and intraprostate DHT concentrations remain stable during aging. Moreover, as proposed by Morgentaler and Traish, the saturation model theory (Morgentaler & Traish, 2009) hypothesize that the prostate is relatively insensitive to serum T level variations in men with normal or mild hypogonadism because the AR receptor in prostate cells is normally saturated by relatively low androgens intratissue concentration. In these conditions, therefore, the AR can be fully activated in spite of the possible decrease in circulating T levels. Moreover, the saturation theory was demonstrated in humans in another recent study conducted by Maggi and coll. that showed that PSA it may represent a new tool in confirming hypogonadism. In particular in this study after adjusting for age, low PSA was associated with hypogonadism-related features (i.e., delayed puberty, lower testis volume) and associated conditions, such as metabolic syndrome, type 2 diabetes, cardiovascular diseases (Rastrelli *et al.*, 2013).

Androgen/androgen receptor and growth factors

Growth factors play a crucial role in the cross-talk between stromal and epithelial cells. These factors, mainly secreted by stromal cells, act in an autocrine/paracrine manner to maintain prostate cellular homeostasis. In addition, numerous experimental studies support the interdependence between growth factors [insulin-like growth factor (IGF), fibroblast growth factor (FGF), transforming growth factor (TGF)] and the intra-prostatic steroid hormone milieu. Alterations of these interactions can modify the balance between cell proliferation and death leading to the development of BPH.

Insulin like growth factor pathway

An important family of growth factors implicated in the development of BPH is insulin-like growth factors (IGF), their receptors and IGF binding-proteins (IGFBP) that regulate the availability of the same factors. IGF-II and IGF receptor type I are expressed at higher levels in stromal cells of BPH compared with normal cells; these changes are followed by a decrease in the levels of IGFBP-2 and by an increased in the levels of IGFBP-5. Other studies have reported that DHT concentrations and IGF-II activity are higher in the stromal cells of the periurethral tissue in BPH patients compared with normal stromal cells (Monti *et al.*, 2001).

In an experimental model of rat in which the AR was suppressed specifically in stromal cells, Yu *et al.* (2011) found a lower prostate epithelial cell proliferation, a decreased AR expression and a decreased IGF-I concentration in stromal cells, suggesting that the AR expressed in these cells may contribute to the development of BPH by regulating the signaling of IGF (Lai *et al.*, 2012).

Fibroblast growth factor pathway

The mitogenic activity of FGF-1, 2, and 7 on prostate epithelial and stromal cells has been shown to correlate with the development of BPH. Both FGF-2 and FGF-7 (also called KGF) are overexpressed in BPH. Moreover, a correlation between epithelial cell proliferation index and FGF-7 levels has been reported in the hyperplastic prostate tissue. Interleukin-1α, produced by prostate epithelial cells, has been hypothesized to be the paracrine factor responsible for the induction of FGF-7 (Giri & Ittmann, 2000).

Transforming growth factor ß1

The transforming growth factor-β (TGFβ1), both in vitro and in vivo, is implicated in the development of BPH by inducing the differentiation of fibroblasts into myofibroblasts and remodeling the stromal cells. It is regarded as a key inducer in the reorganization of pathogenic prostatic stromal cells (Sampson *et al.*, 2013). Its effects are mediated by an alteration of the different components of the IGF-I axis, in particular by the induction of the protein IGFBP-3, whose levels are particularly high in the stromal cells of BPH. In addition, TGFβ1 is mainly located in the epithelial cells of BPH and its expression is higher in BPH tissue compared with normal tissue (Sampson *et al.*, 2013). Thus, the secretion of TGFβ1 regulates epithelial cell response to IGF-I stromal cell–cell interaction and this again reflects the complexity of the interactions stroma-epithelium underlying the development of prostate disease.

BENIGN PROSTATE HYPERPLASIA: ROLE OF THE ESTROGEN PATHWAY

Estrogens regulate their effects at the level of the target cells through interaction with estrogen receptors (ER). Both ER-α and ER-β, similarly to the AR, are transcription factors[24]. ER-β is similar to ER-α in DNA-binding and ligand domains, but differs for the N-terminal transactivation domain. The role of estrogen in the pathogenesis of BPH is based on the observation that treatment of dogs with estrogen (in addition to androgens) leads to the development of BPH and LUTS BPH-related (Coffey & Walsh, 1990).

In men, while serum androgen levels decrease during aging, the levels of 17ß-estradiol (E_2) remain constant increasing the ratio E_2/T. This altered relationship is clearly associated with the development of the disease BPH/LUTS (Roberts *et al.*, 2004). Some authors have shown a correlation between serum estrogen levels and the prostate volume (Hammarsten *et al.*, 2009). Finally, E_2 levels in the stromal cells of BPH patients increase during aging, and this seems to be associated with a high expression of aromatase, the enzyme that converts androgens into estrogens (Ho *et al.*, 2008). However, previously, other authors had not shown the same results (Negri-Cesi *et al.*, 1998).

The role of ER-α and ER-β in the pathogenesis of BPH is not yet fully understood. It is thought that the two receptor subtypes may perform different functions depending on the interaction with different ligands, changes in the balance between classical and non-classical signaling, and interactions with different co-repressors and co-activators. In general, activation of ER-α in the prostate is associated with hyperplasia and inflammation (Nicholson & Ricke, 2011). In addition, the epithelial-to-mesenchymal transition is an important mechanism in the etiology of BPH and ER-α plays a crucial role in this mechanism (Shao *et al.*, 2014); while ER-β are located in the epithelial cells (Macoska, 2011), ER-α are primarily found in stromal cells. ER-β is associated with antiproliferative activity, indeed, ER-β knockout mice develop hyperplasia of the stromal cells during aging. Moreover, in rats, neonatal exposure to diethylstilbestrol cause prostatic hyperplasia and dysplasia, which probably results from an up-regulation of ER-α and down-regulation of ER-β. Finally, it has been reported that the activation of ER-β causes apoptosis in BPH with an androgen-independent mechanism (McPherson *et al.*, 2010). The epithelium-stroma interactions mediated by growth factors are well-known, while the role of estrogen in these interactions is not yet clear. However, it is known that the ER-α, expressed in stromal cells, induces the secretion of growth factors that act in a paracrine manner stimulating the proliferation of epithelial cells (Shao *et al.*, 2014); ER-α also seems to cause a proliferative effect on stromal cells.

In conclusion, further research is needed to clarify definitively the role of signaling estrogen/ER in the development of BPH.

BENIGN PROSTATE HYPERPLASIA: ROLE OF PROLACTIN

The role of PRL in andrology was recently revisited in a review of Maggi and coll., illustrating implications for low PRL concerning reproduction, sexuality, metabolism, and psychological health (Rastrelli *et al.*, 2015).

Prolactin is best known for its action on the female mammary gland; however, circulating hormone is also detected in males and its receptors (PRLR) are expressed in prostate, hence, prostate is a target of this hormone.

In the study of Wennbo and coll. three lines of PRL transgenic mice were generated having serum levels of PRL of approximately 15, 100, and 250 ng/mL, respectively. These mice developed dramatic enlargement of the prostate gland, approximately 20 times the normal prostate weight (Wennbo *et al.*, 1997).

Although, the physiological role of PRL on prostate and on development on BPH has been studied mainly in animal model, its role is yet unclear. PRL can directly stimulate proliferation and inhibit apoptosis of prostate epithelial cells (Goffin *et al.*, 2013) in a Stat5-mediated manner.

Prolactin action on rodent prostate was not well investigated until the generation of metallothionein (Mt) PRL transgenic mice, that expressed PRL at systemic level. In this mice model, prostate enlarges significantly, but they have also elevated serum T levels that could mask the real PRL effect on the gland (Lai *et al.*, 2013). In Mt PRL mice, after few weeks of PRL overexpression, prostate shows classical features of BPH, such as stromal hyperplasia and focal area of dysplasia (prostate intraepithelial neoplasia: PIN), and these changes are independent of androgens levels (Goffin *et al.*, 2013).

To investigated whether hyperprolactinemia was associated with prostate enlargement in humans, in Colao and colleagues conducted a pilot observational, prospective, case–control study on 20 men with prolactinomas and 20 age-matched healthy control (Colao *et al.*, 2004). The authors concluded that PRL excess decreased prostate size, probably reducing serum T and DHT levels; after 24 months of treatment with cabergoline, the prostate volume normalized. However, the patients studied had lower androgens levels than the controls, so the real effect of hyperprolactinemia could not be evaluated.

To avoid that androgens conceal the real effect of PRL, more recently a new transgenic mouse model (probasin-PRL) has been generated. This experimental model, which has PRL expressed only within the prostate, shows prostate hypertrophy, stromal expansion, ductal dilatation, and focal epithelial dysplasia, feature similar to those characteristic of BPH in humans (Lai *et al.*, 2013). Interestingly, in a rat model of chronic hyperprolactinemia induced by dopamine antagonist administration, prostate showed a marked enlargement (Van Coppenolle *et al.*, 2001). A similar effects on epithelial cells was also reported in cell cultures derived from human BPH specimens; in these samples, the expression of PRL receptors was not increased compared with normal prostate samples (Goffin *et al.*, 2013). Another interesting aspect is the evidence in favor of the correlation between chronic prostate inflammation and BPH; it is possible that PRL, in mice, causes an estrogen-mediated prostate inflammation, that is not observed in estrogen-deficient aromatase knockout mice, despite elevated serum levels of PRL (Goffin *et al.*, 2013). Thus, increased serum PRL levels alone are not sufficient to exert proinflammatory effects.

In conclusion, it is not clear whether prostate autocrine PRL expression is increased in BPH and so far there are not strong evidences supporting a role of this hormone in promoting BPH. Finally, it is relevant to report that there are some evidences suggesting a possible role of PRL on prostate cancer development (Giuffrida *et al.*, 2010).

BENIGN PROSTATE HYPERPLASIA AND INFLAMMATION

The development of BPH is closely related to an inflammatory microenvironment. The activation, recruitment, and proliferation of immune competent cells are a significant component of the disease: the inflammatory component. Several studies have shown that the prostate stromal component in patients with BPH is able to produce various chemokines (especially of the group of CXC) that attract immune system cells (monocytes, B and T lymphocytes) within the prostatic tissue. Lymphocytes and macrophages produce IFN-γ and IL-17 which stimulate the production of chemokines by stromal cells; these interactions appear to be responsible for prostate cell proliferation and the development of BPH (Macoska, 2011). It is still unclear whether

prostate hyperplasia causes inflammation or whether, instead, the development of BPH is caused by a pre-existing inflammatory status. Numerous clinical studies have shown that patients with prostatitis have higher chances of developing BPH/LUTS supporting, thus, the hypothesis that inflammation may lead to the development of BPH. Chronic inflammation, which generally follows an acute inflammatory process caused by infectious agents, is favored by hormonal or metabolic abnormalities (Mohanty & Jolly, 1996; Nickel, 2006; Wu *et al.*, 2008; Ma & Zhang, 2010; Edlin *et al.*, 2012; Mitteregger *et al.*, 2012; Hung *et al.*, 2013).

Prostate immune competent cell activation stimulates the proliferation of other immune competent cells thus leading to an increase in the production of several inflammatory cytokines and chemokines (Vignozzi *et al.*, 2014). The prostatic stromal cells, which act as a target of infectious agents through activation of toll-like receptors (TLR) and afterward as antigen-presenting cells (APCs), play a crucial role in the induction of the inflammatory response and the consequent development of prostatic hyperplasia. These cells respond to cytokines IFN-γ, IL-2, and IL-17 released by lymphocytes by increasing the production of IL-8 and IL-6, which are the main cause of the growth in the stromal BPH.

The mechanisms leading inflammation development and chemokines/cytokines overexpression/production within prostate during aging are not still completely known. However, a close correlation between these mechanisms and the alterations in the metabolism or sex steroid levels (androgen/estrogen ratio) have been shown. In particular, Vignozzi and colleagues reported a typical prostate inflammatory phenotype and tissue remodeling accompanied by low serum T levels (and high serum E_2 levels) in male rabbits with metabolic syndrome (MetS) (Vignozzi *et al.*, 2012; Corona *et al.*, 2014), suggesting a key role of hypogonadism in the development of prostate inflammation. Accordingly, the administration of T to this experimental model of MetS overcomes the major prostate alterations induced by MetS. These observations suggest that, in hypogonadal patients with prostate inflammation, treatment with T may neutralize the inflammatory process and, therefore, the possible subsequent development of BPH/LUTS. However, as recently we reported (Condorelli *et al.*, 2014), the main difference between the inflammation of the male accessory glands (such as the prostate) and the BPH is that the last condition is a disease characterized by hyperplasia that depends by the action of androgens, in particular of DHT.

BENIGN PROSTATE HYPERPLASIA AND METABOLIC SYNDROME

The metabolic syndrome (MS) represents a risk factor for the development of BPH. The mechanisms responsible for this association are different, in particular they are represented by the role of the insulin resistance, the hormonal alterations, the pelvic atherosclerosis, and the local inflammation. Especially the hyperinsulinism is associated with stimulation of the receptor for IGF-1, higher IGF-1 level, and lower IGF-1 binding, high cytosolic-free calcium in smooth muscle and neural cells, activation of the sympathetic nervous system and increase in the prostatic smooth muscle tone. From the hormonal point of view, the fundamental element is represented by the alteration of the estrogens–androgens ratio in the peripheral circulation. Atherosclerosis is associated with ischemia of the prostate tissue and bladder tissue. Finally, this condition is associated with increased local production of key proinflammatory cytokines (Rohrmann *et al.*, 2005; De Nunzio *et al.*, 2012; Wang *et al.*, 2012; Lotti *et al.*, 2013; Corona *et al.*, 2014; Vignozzi *et al.*, 2014). From the therapeutic point of view this knowledge suggest the use of insulin sensitizing drugs for the treatment of this condition (Murff *et al.*, 2014; Mosli *et al.*, 2015).

VITAMIN D AND BENIGN PROSTATIC HYPERPLASIA

Several evidences have shown important connections between the metabolism of vitamin D and the risk of developing BPH. In particular epidemiological data suggest a higher prevalence of BPH in patients with hypovitaminosis (Haghsheno *et al.*, 2013), and the vitamin D receptor has been identified as a potential therapeutic target in patients with BPH (Adorini *et al.*, 2010; Manchanda *et al.*, 2012). Agonists for the vitamin D receptor (e.g., Elocalcitol) have also demonstrated anti-inflammatory efficacy on prostatic urethra that express receptor for vitamin D and is functionally involved in the development of inflammatory disorders (Comeglio *et al.*, 2010). The symptoms of BPH are also related to hypertrophy and vesical hyperactivity, in particular the receptor for vitamin D has also been identified in the bladder, with response to agonists, such as for example: calcitriol

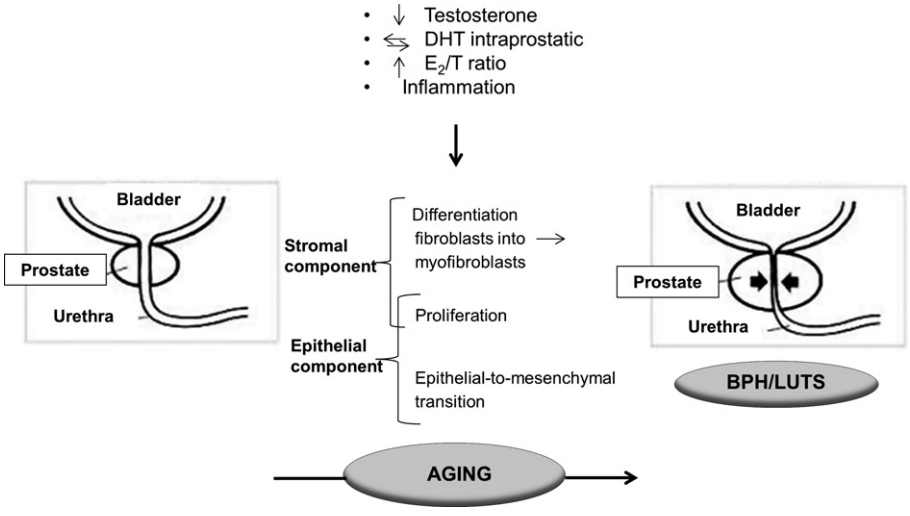


Figure 2 Schematic representation of the multifactorial pathogenesis of BPH/LUTS.

Table 1 Endocrine regulation of benign prostatic hyperplasia. Main mechanisms and supporting studies

Analyzed mechanism	Bibliographical reference
Signaling pathway androgen/androgen receptor	Nicholson T.M. & Ricke, W.A. Differentiation 82, 184–99 (2011). Roehrborn C.G. Int J Impot Res 20 Suppl 3, S11–8 (2008). Vignozzi L. et al. J Endocrinol 212, 71–84 (2012). Carson C., 3rd & Rittmaster, R. Urology 61, 2–7 (2003). Corona G. et al. J Endocrinol Invest 34, 232–43 (2011). Harman S.M. et al. J Clin Endocrinol Metab 86, 724–31 (2001). Corona G. et al. Int J Endocrinol 2014, 329456 (2014). Shigehara K. et al. Aging Male 14, 53–8 (2011) Imperato–McGinley J, Zhu YS. Mol Cell Endocrinol. 30;198:51–9 (2002). Lai K.P. et al. Mol Endocrinol 27, 1617–31 (2013). Barkin J. Can J Urol 18 Suppl, 14–9 (2011). Morgentaler A. & Traish, A.M. Eur Urol 55, 310–20 (2009). Rastrelli G. et al. J Sex Med. 10:2518–28 (2013).
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Role of metabolic syndrome	De Nunzio C. et al. Eur Urol 61:560–570 (2012). Lotti F. et al. Asian J Androl 16:295–304 (2013). Rohrmann S. et al. Int J Obes (Lond) 29:310–316 (2005). Wang S. et al. Prostate Cancer Prostatic Dis 15:265–272 (2012). Corona G. et al. Int J Endocrinol 2014, 329456 (2014). Vignozzi L. et al. J Endocrinol 212, 71–84 (2012).
Role of Vitamin D	Haghsheno MA. et al. J Urol.;190:608–14 (2013). Manchanda PK. et al. Indian J Urol. 28:377–81 (2012). Adorini et al. Ann N Y Acad Sci.1193:146–52 (2010). Comeglio et al. Endocrinol Invest. 33:730–8 (2010). Espinosa et al. Can J Urol. 20:6820–5 (2013). Tavani A. et al. Eur Urol. 50:549–54 (2006).

and BXL-628 (synthetic derivative with minor action on the calcium levels). Therefore, it has been suggested a therapeutic use of BXL-628 for the reduction in bladder irritation (Crescioli *et al.*, 2005).

The prevalence of hypovitaminosis among men with BPH is high (Espinosa *et al.*, 2013), suggesting the presence of possible pathophysiological connections. Especially vitamin D modulates several functional systems involved in the pathogenesis of BPH: inhibitory effect on the RhoA/ROCK pathway, along with cyclooxygenase-2 expression and prostaglandin E2 production in BPH stromal cells (Espinosa *et al.*, 2013). An intake of vitamin D (6000 IU/day) was associated with a reduction in prostate volume in patients with BPH (Espinosa *et al.*, 2013). However, about this aspect, the data appear contradictory, in fact a multicenter Italian study on 1369 men with BPH surgically treated it showed no protective effect of dietary intake of vitamin D (Tavani *et al.*, 2006).

Also the BPH supported by the activation of inflammatory and hormonal stimuli, such as: testosterone, DHT and IGF-1, IL-8 is counteracted by vitamin D (Espinosa *et al.*, 2013). Another aspect further elaborated in the literature is the role of the main polymorphisms of the gene for the vitamin D receptor and the risk of developing BPH. A recent meta-analysis examined the role of four polymorphisms: Taq-I-Bsm I, Apa-I, and Fok-I, showing a lack of association between them and the risk of BPH in Caucasians and Asian population (Zeng *et al.*, 2014).

Table 1 summarizes the main scientific evidence on the main endocrine mechanisms regarding the benign prostatic hyperplasia.

CONCLUSION

Overall, the data of the literature suggest that the pathogenesis of the BPH is influenced by different hormonal mechanisms, in particular: the androgens and the activity of their receptor, the role of growth factors and the importance of the estrogen metabolism. Moreover, other aspects must be considered such as the chronic inflammation, the effects of the metabolic syndrome and the modulation exerted by vitamin D. In clinical terms, the knowledge of these mechanisms suggests new perspectives of diagnostical and therapeutical management for these patients (Fig. 2).

CONFLICT OF INTEREST

Each author declare no conflict of interest.

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