SEXUAL MEDICINE REVIEWS REVIEW

Testosterone and Benign Prostatic Hyperplasia

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ABSTRACT

Introduction: Benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) are frequent in aging. Nonetheless, their pathogenesis is largely unknown. The androgen dependence of the first phases of prostate development have inspired the historical view that higher testosterone (T) may be involved in BPH occurrence; however, recent evidence suggests a different scenario.

Aim: To review the available knowledge on the pathogenesis of BPH particularly concerning the role of T and the possible connections with metabolic impairments.

Methods: Relevant records were retrieved by an extensive search in Medline, including the following keywords ("testosterone"[MeSH Terms] OR "testosterone"[All Fields]) AND ("prostatic hyperplasia"[MeSH Terms] OR ("prostatic"[All Fields] AND "hyperplasia"[All Fields]) OR "prostatic hyperplasia"[All Fields] OR ("benign"[All Fields] AND "prostatic"[All Fields] AND "hyperplasia"[All Fields]) OR "benign prostatic hyperplasia"[All Fields]). There were no limitations in terms of publication date or study design.

Main outcome measures: Preclinical and clinical studies have been reported, with special emphasis on our contribution and interpretation.

Results: Inflammation is a key aspect of BPH development. Along with infectious agents, prostate inflammation can be triggered by metabolic stimuli, such as dyslipidemia, an important component of metabolic syndrome (MetS). Low T and hyperestrogenism frequently occur in MetS. Mounting evidence shows that low, rather than high, T and hyperestrogenism may favor prostate inflammation. Considering these data as a whole, we postulate that BPH is the result of the action of multiple factors, which reinforce their mutual detrimental effects.

Conclusion: T is not detrimental for the prostate, and treating hypogonadism could even produce relief from LUTS and limit prostatic inflammation, which generates and maintains the process leading to BPH. **Rastrelli G, Vignozzi L, Corona G, et al. Testosterone and Benign Prostatic Hyperplasia. Sex Med Rev 2018;XX:XX–XX.**

Key Words: Benign prostatic hyperplasia; Testosterone; Androgens; Inflammation; Dyslipidemia; Metabolic syndrome

INTRODUCTION

Role of Androgens in Prostate Development

The differentiation of prostate tissue during early fetal life is a process known as "branching morphogenesis" involving the arborization of epithelial buds from the urogenital sinus into the surrounding mesenchymal tissue.[1] The process involves mostly the epithelial cells but is driven by the mesenchyme. Studies using recombinant tissues made of wild-type epithelium and androgen receptor (AR)-deficient mesenchyme have shown that the action of androgens on mesenchymal cells is necessary for prostate differentiation.[2] Conversely, the prostate develops normally when recombinant tissues are made of AR-deficient epithelium and wild-type mesenchyme.[2]

Further evidence for the role of androgens in the early development of the prostate comes from the observation that in female rats, the ventral mesenchymal pad forms similarly to that in males; however, a normal prostate develops only when females are administered androgens.[3] The link between AR-stimulated mesenchymal cell and epithelial bud formation, elongation, and arborization is still controversial. Several growth factors, acting in a paracrine manner, are involved in the process and are collectively termed andromedins. The term andromedin implies

Received August 31, 2018. Accepted October 18, 2018.

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https://doi.org/10.1016/j.sxmr.2018.10.006

that they are somehow androgen-dependent. However, whether their secretion is stimulated by the AR action or whether androgens are indirectly involved in their activity or availability remains controversial.[4]

The activity of the AR on epithelial cells likely occurs only at a later stage of differentiation, because this activity is necessary for the cells' exocrine secretory function[5] and for the differentiation from basal to terminal differentiated luminal cells.[6]

Role of Androgens in Prostate Growth

Besides differentiation, androgens are also involved in prostate proliferation. Prostate proliferation passes through 3 waves of growth.[1] The first wave occurs during fetal life, the second takes place during puberty, and the last begins at midlife and proceeds throughout senescence. The first and the second waves temporally correspond to an increase in testosterone (T) levels. In fact, T levels in male fetuses begin to increase at the 8th week of gestation, peak at the 16th week at a concentration similar to that seen in adulthood, and slowly decline thereafter to the low levels detected at birth. Shortly after birth, T increases again for a 6-month period, known as "mini-puberty," and then declines to undetectable levels during childhood.

This early life androgenic milieu is responsible for the differentiation of male external and internal genitalia, including the prostate. Prostate differentiation and growth start at the 10th–12th week of gestation[7] and are completed at birth, when the gland weighs approximately 2 g.[1] Paralleling the decline of circulating T levels after mini-puberty, prostate volume decreases slightly,[8] and its growth is quiescent until puberty, when the second wave of growth occurs in response to the increase in circulating T. During early stages of puberty, the prostate reaches 10 g, and after the completion of pubertal development, it weighs approximately 20 g.[1]

In contrast to most organs, the prostate keeps growing during adult life. In fact, after early adulthood, during which its volume remains steady, the prostate starts enlarging in middle age and continues to enlarge in the elderly period.[1] However, the third wave of growth differs from the previous 2 waves in that proliferation affects only the transitional zone, rather than the entire gland as in the previous waves. In addition, whereas in the previous 2 waves, the growth paralleled a physiological increase in circulating T, the third wave corresponds to the start of the age-related decline in T.[9] Accordingly, data from epidemiologic studies did not demonstrate an association between higher circulating T levels and benign prostatic hyperplasia (BPH).[10,11]

The Paradox of Declining T and Prostatic Hyperplasia During Aging

This paradox still does not have an explanation; however, some hypotheses can be advanced. First is the saturation hypothesis,[12] which surmises that the prostate is sensitive to a change in androgen level when it occurs in the severe hypogonadal range, but this sensitivity is lost when the value corresponds to mild hypogonadism or eugonadism. This effect could be due to saturation of the available AR on the gland, which would become unresponsive to further increases in T levels.[12] According to this hypothesis, in a population of 3156 patients with a mean age of 52.5 years consulting for sexual dysfunction, we found that the relationship between circulating total T and prostate-specific antigen (PSA) is better described by a sigmoid curve plateauing around a T concentration of 8 nmol/L.[13] Below this threshold, T is in the severe hypogonadal range and small changes correspond to greater variations in PSA.[13] Other hypotheses take into account that T, besides having a direct hormonal function, plays out part of its broad actions through its metabolites, including dihydrotestosterone (DHT) and estradiol (E_2). The actions mediated by DHT or estrogens could mask the relationship between T and BPH.

DHT binds the AR with a 3-fold greater affinity than T. It is synthesized from T by the activity of the enzyme 5-alpha reductase, whose isoform 2 is abundantly expressed by prostate tissue, whereas the isoform 1 is less specific and more broadly expressed in human tissues. DHT acts mostly in a paracrine manner, as suggested by an intraprostatic DHT:T ratio on the order of 8 in normal prostate tissue,[14] which is significantly higher than the circulating DHT:T ratio of approximately 0.1 in middle-aged and elderly community-dwelling men.[15] It could be then hypothesized that intraprostatic DHT levels are not adequately mirrored by circulating T levels. In addition, it should be noted that in BPH, intraprostatic androgen levels do not differ from those in normal prostates,[14] corroborating the idea that the third wave of prostate enlargement is not a function of higher T levels.

E_2 is the other metabolite of T, synthesized by the enzyme aromatase, which along with fat is expressed in the urogenital tract.[16] Estrogen receptors α and β (ERα and ERβ) are expressed in the prostate. ERα is detected mainly in the stromal cells, and its selective stimulation is associated with prostate hyperplasia and inflammation,[17] whereas ERβ is typical of the epithelium, and its knockout results in prostate hyperplasia.[18] Prostate stromal cells also express the membrane estrogen receptor G protein-coupled receptor 30 (GPR30) or G protein-coupled estrogen receptor (GPER), the stimulation of which appears to be the major effector of the estrogen-mediated inflammatory alterations detected in BPH in both experimental animal models and humans.[19]

Although the role of estrogens in the pathogenesis of BPH is far from being elucidated, some epidemiologic studies,[20–23] but not all,[24] have found an association between higher serum estrogen level or estrogen/androgen ratio and BPH. Accordingly, there is evidence that aromatase inhibitors, which block the conversion of androgens to estrogens, can prevent prostatic hyperplasia. In a monkey model of BPH induced by treatment with androstenedione, the aromatase inhibitor atamestane was able to prevent the development of the histological features of BPH.[25] These encouraging results have not translated into clinical practice, however; randomized clinical trials in men with BPH[26,27] and

older men with hypogonadism[28,29] did not show any significant improvement in urinary symptoms or urodynamic parameters associated with aromatase inhibitor treatment compared with placebo. Similar to aromatase inhibitors, selective estrogen receptor modulators (SERMs) have shown antiproliferative effects on prostate tissue of dogs with hormonally induced[30] or naturally occurring BPH.[31] However, further research evaluating the use of SERMS in clinical practice has not been reported to date, and their effectiveness in improving urinary symptoms and function in men with BPH men remains unclear.

Starting from this contradictory and inconclusive evidence of the role of T in prostate growth, in the present review, we summarize the available knowledge on the pathogenesis of BPH and the possible role of T in this process. We include data from both preclinical and clinical studies.

METHODS

An extensive search in MEDLINE was performed using the following keywords: ("testosterone"[MeSH Terms] OR "testosterone"[All Fields]) AND ("prostatic hyperplasia"[MeSH Terms] OR ("prostatic"[All Fields] AND "hyperplasia"[All Fields]) OR "prostatic hyperplasia"[All Fields] OR ("benign"[All Fields] AND "prostatic"[All Fields] AND "hyperplasia"[All Fields]) OR "benign prostatic hyperplasia"[All Fields]). There were no limitations in terms of publication date or study design. Concerning the topic of the relationship between metabolic syndrome (MetS) and BPH, we conducted a separate search including the following terms: ("metabolic syndrome"[MeSH Terms] OR ("metabolic"[All Fields] AND "syndrome"[All Fields]) OR "metabolic syndrome"[All Fields]) AND ("prostatic hyperplasia"[MeSH Terms] OR ("prostatic"[All Fields] AND "hyperplasia"[All Fields]) OR "prostatic hyperplasia"[All Fields] OR ("benign"[All Fields] AND "prostatic"[All Fields] AND "hyperplasia"[All Fields]) OR "benign prostatic hyperplasia"[All Fields]). Since preclinical and clinical data on this topic identified a relevant role for dyslipidemia in favoring prostatic inflammation, a specific search for clinical trials on the effect of statins on BPH was conducted using the following keywords: ("hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action] OR "hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR ("hydroxymethylglutaryl-coa"[All Fields] AND "reductase"[All Fields] AND "inhibitors"[All Fields]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[All Fields] OR "statins"[All Fields]) AND ("prostatic hyperplasia"[MeSH Terms] OR ("prostatic"[All Fields] AND "hyperplasia"[All Fields]) OR "prostatic hyperplasia"[All Fields] OR ("benign"[All Fields] AND "prostatic"[All Fields] AND "hyperplasia"[All Fields]) OR "benign prostatic hyperplasia"[All Fields]), limiting the search to clinical trials.

BPH

As mentioned above, BPH is considered the third wave of prostate growth, with different characteristics than the previous 2 waves. BPH is defined as hyperproliferation of the stromal component and, to a lesser extent, the epithelial component of the prostate, which usually manifests as an enlargement of the gland, known as benign prostatic enlargement (BPE). BPH is infrequent before age 40 years, but its prevalence increases sharply in the subsequent decades, reaching 40%−50% at age 50−60 years and 80%−90% after age 80 years.[32] BPH is considered a histological diagnosis, even though a biopsy is not routinely required. In fact, in clinical practice, BPH is a presumptive diagnosis based on the presence of lower urinary tract symptoms (LUTS) and diffusely enlarged prostate with dense consistency at digital rectal examination.

Although LUTS are typical symptoms of BPH, there are asymptomatic men with BPH and, conversely, men with LUTS not related to BPH.[33] Paralleling the age-related prevalence in BPH, the incidence of LUTS increases with aging. In particular, 50% of men age >50 years complain of LUTS, increasing to 80% at age 80 years.[32,34] The relationship between BPH and LUTS is explained in part by an obvious mechanical impairment due to BPE, which exerts pressure on the urethra and bladder, leading to difficulties in urination of increasing severity up to urinary obstruction (benign prostate obstruction). However, BPH and LUTS are more than plumbing problems; in fact, inflammation is a pivotal mechanism linking these conditions.

BPH, LUTS, AND INFLAMMATION

The prostate is characterized by an organized immunocompetent tissue that includes several immunocompetent cells, including lymphocytes, macrophages, and granulocytes that together compose the prostate-associated lymphoid tissue (PALT). This tissue, which is similar to that present in other areas of the body exposed to external agents (eg, tonsils for the upper airways, appendix for gut), is intended for the response to infectious pathogens. Indeed, the male lower urinary and genital tract are exposed to frequent bacterial infections, both symptomatic and asymptomatic.

In the prostate, the response to infectious agents is represented by the activation of PALT. However, activated PALT has the potential to set up a chronic immune response, which persists even when the primary proinflammatory agent has been removed. The process begins with the expansion of the T helper 1 (Th1) lymphocyte infiltrate within the PALT in response to an acute proinflammatory stimulus, such as bacterial infections. Th1 lymphocytes are characterized by the secretion of INF-γ and IL-2 and these are the main cytokines found in early stages of BPH.[35] Th1 lymphocytes, through INF-γ and IL-2, stimulate prostate stromal cells to produce IL-15, which in turn supports the survival of the lymphocyte infiltration, favoring the maintenance of an immune response, which becomes chronic. It is hypothesized that during chronic inflammation, a progressive switch towards a Th2 immune response occurs, as suggested by the increased secretion of IL-4 and IL-13 seen in the later stages of BPH.[35] In addition,

increased production of IL-17, proportional to IL-15 levels, is found in BPH tissue,[36] suggesting a shift toward a Th17 lymphocytic phenotype characteristic of autoimmune diseases. Interestingly, the increase in IL-17 has been associated with increased prostate stromal cell secretion of IL-6 and IL-8,[36] which are key factors in the hyperplasia of stromal prostatic cells themselves.[37] Considered together, these mechanisms suggest that frequent infectious stimuli could represent a priming for a cascade of immune events primarily intended to limit bacterial infection. However, the protracted process activates different immune and autoimmune responses, which are able to self-maintain the immune mechanisms while also favoring the hyperproliferation of stromal prostatic cells, leading to BPH and eventually to BPE.

Along with the immune response to infectious stimuli of professional immune cells, it has been demonstrated that prostate stromal cells have the potential to acquire the phenotype of antigen-presenting cells (APCs).[38] Stromal cells react to inflammatory stimuli, such as lipopolysaccharide, through the activation of Toll-like receptors (TLRs), which mediate the secretion of several cytokines, including IL-6, IL-8, and the INF-γ-induced protein 10 (IP-10).[38] In addition, consistent with APC activity, stromal BPH cells induce the proliferation of alloreactive $CD4^+$ T cells and their secretion of INF-γ and IL-17.[38] Thus, human BPH cells as APCs are able to stimulate $CD4^+$ T lymphocyte activity; however, the reverse mechanism has also been demonstrated. In fact, coculturing human BPH cells with activated $CD4^+$ T lymphocytes is able to increase the spontaneous secretion in BPH cells of several key cytokines—including IL-8, IL-6, IL-17, IP-10, IL-12, MCP1, eotaxin, and IL-15—and a number of growth factors—including basic fibroblast growth factor, vascular endothelial growth factor, and platelet-derived growth factor BB—by more than 2 log units.[39] Overall, these data suggest cross-talk between stromal cells and immune T cells in prostate tissue. In this context, the presence of a proinflammatory agent, such as a bacterial infection, can induce an immune response (Th1) that if chronically maintained could cause the shift of T cells toward a profile (Th2/Th17). A role of the urinary microbiome in the inflammatory process has been suggested recently.[40] The urine and semen of men with chronic prostatitis have greater representation of *Clostridia* and *Bacteroides* compared with healthy men, whose main microbes are *Lactobacillus* and *Staphylococcus*.[40] It could be hypothesized that this dysbiosis can favor the self-maintenance of inflammation within the prostate,[40] although this requires further investigation. Irrespective of the process, the Th2/Th17 shift of the immune response within the prostate is able to induce hyperplasia of stromal prostate cells. Stromal prostate cells in turn have the potential to act as APCs and can enhance the activation of T cells in response to inflammatory stimuli, thus perpetuating the inflammatory response on one hand while favoring the hyperplasia of stromal tissue on the other hand.

BPH, LUTS, AND INFLAMMATION: EVIDENCE FROM CLINICAL STUDIES

Clinical evidence of the great importance of inflammation in BPH and LUTS has been provided recently by the longitudinal results of the Medical Therapies of Prostate Symptoms (MTOPS) study. In the biopsy MTOPS substudy, involving 859 men, a stronger inflammation in the transitional zone, as measured by the immunopositivity to CD4, CD8, CD45, and CD68, was associated with worse BPH in terms of progression of LUTS and incidence of acute urinary retention or urinary incontinence, during a median follow-up of 4.8 years.[41] In the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, involving 8224 men randomized to dutasteride 0.5 mg daily or placebo for 4 years, chronic inflammation at baseline was associated with a greater prostatic volume and worse LUTS.[42] The trial's longitudinal results show that among 4109 men who received placebo, those with chronic inflammation at baseline biopsy experienced a greater increase in prostate volume,[43] a higher incidence of acute urinary retention[43] and more severe deterioration in chronic prostatitis/chronic pelvic pain syndrome-like symptoms.[44]

Although the role of inflammation in the pathogenesis of BPH and LUTS is now well established, the etiologic conditions and risk factors involved in initiation of the inflammatory process remain largely unknown. Several lines of evidence suggest that metabolic and hormonal factors could contribute to the development and progression of inflammation in the prostate, leading to BPH, BPE, and LUTS.

METS AND BPH

Suggestions from Epidemiologic Studies

MetS is a cluster of metabolic derangements that have insulin resistance as the common pathogenic mechanism. Increasing evidence from epidemiologic studies shows an association between MetS and BPH. In a recent large British study based on a healthcare database and involving more than 170,000 men, the risk of MetS was 37% higher in men with a clinical diagnosis of BPH compared with those without BPH.[45] In a meta-analysis of 8 studies and a total of 5403 men, patients with MetS had a significantly greater prostate volume, with the major difference seen in the transitional zone, which was on average almost 4 mL greater in the MetS patients compared with their non-MetS counterparts.[46] The difference in prostate volume was even more evident in men with a worse lipid profile, given the significant negative correlation between high-density lipoprotein (HDL) cholesterol level and prostate volume.[46] The strong association between dyslipidemia and BPE has been confirmed in 2 more recent Italian multicenter studies[47,48] involving, respectively, 379 and 224 men consulting for LUTS due to BPE. In these studies, lower HDL cholesterol and higher triglyceride levels were associated with greater total prostate volume,[47,48] and lower HDL cholesterol was also significantly related to an

increased transitional zone volume and a higher prevalence of intravesical prostate protrusion.[48] The associations among prostate enlargement, MetS, and dyslipidemia have been further confirmed in a population of 1823 men with a mean age of 54.7 ± 11.4 years seeking medical care for sexual dysfunction.[49]

Although the relationship between MetS and BPH is based mainly on observational studies with a limited possibility of establishing a causal relationship between these conditions, a study of young patients may could help in providing some insight. In a consecutive series of 171 men (mean age, 36.5 ± 8.3 years) seeking medical care for infertility, the presence of a greater number of MetS components was associated with a greater prostate volume and with increases in several markers of prostate inflammation, including higher seminal IL-8 levels, higher arterial prostatic peak systolic velocity, and prostate inhomogeneity evaluated at transrectal prostate ultrasound.[50] In that study, HDL cholesterol was confirmed as the strongest correlate of prostate volume among the MetS components, whereas the inflammatory parameters were mainly associated with visceral obesity.[50]

Replicating the finding of a relationship between MetS and prostate volume in a population without BPH provides indirect evidence that MetS is a determinant of prostate enlargement, and that the pathogenic process likely occurs early in life, several years before the appearance of BPH and its related symptoms. However, what is the pathogenic mechanism that links MetS and BPH? As mentioned above, inflammation is recognized as a cornerstone in the development of BPH, and MetS is characterized by a systemic low-grade inflammation. In the Prostate Cancer Prevention Trial (PCPT), among men randomized to the placebo arm and free from BPH at baseline (n = 4971), new occurrence of BPH over a follow-up of 10 years was predicted by higher serum levels of C-reactive protein and IL-6 at baseline.[51] This suggests that conditions characterized by systemic inflammation, such as MetS, might be implicated in the development of BPH.

Evidence from Preclinical Studies

Experimental proof for the role of MetS in inducing prostate inflammation and hyperplasia eventually leading to BPH and LUTS has been provided by a rabbit model of MetS developed in our laboratory.[52] These animals, which were fed a high-fat diet (HFD) for 12 weeks, developed several metabolic alterations, including dyslipidemia, accumulation of visceral fat, glucose intolerance, and hypertension, recapitulating the clinical picture of MetS. Interestingly, compared with rabbits fed a regular diet, the HFD rabbits were characterized by bladder inflammation and fibrosis, corresponding to dysfunction in contractile/relaxant mechanisms of smooth muscle cells.[53] Moreover, the HFD was associated with the development of several alterations in the prostate, which was characterized by an increased expression in inflammation- and fibrosis-related genes.[54] Consistently, in the HFD rabbits, the histological evaluation of prostate tissue showed increased leucocyte infiltration rich in neutrophils and $CD4^+$ and $CD8^+$ lymphocytes, along with depletion of smooth muscle tissue substituted by collagen fibers.[54] The expression levels in the prostate of inflammation-related genes, such as *tumor necrosis factor (TNF)-α, IL-6, TLR-2, TLR-4, RAR-related orphan receptor γt (RORγt)*, and *6-transmembrane protein of prostate 2 (STAMP2)*, were increasingly higher according to the number of MetS components developed by rabbits.[55]

In humans, the association between MetS components and inflammatory features in the prostate has been proven in a study on 244 men who underwent prostate surgery for BPH.[56] The histopathological examination showed inflammatory features in all the BPH specimens; however, the CD45 positivity and the degree of the inflammation, evaluated by an inflammatory score based on anatomical localization, grade and extent of inflammatory infiltrate, was more severe in BPH men with MetS, with a significantly greater stepwise severity according to the number of MetS components.[56] Interestingly, among the MetS components, only low HDL cholesterol and hypertriglyceridemia were significantly associated with higher inflammatory scores and CD45 positivity.[56] This is in line with the previously reported data from epidemiologic studies and strongly suggests a pathogenic role for high lipids in the predisposition to worse inflammatory lesions within prostate tissue. To verify this hypothesis, human stromal cells from BPH tissue were treated in vitro with oxidized low-density lipoprotein (LDLox). The treatment produced a significant enhancement of several cytokines and growth factors, including IL-6, IL-8, IL-7, basic fibroblast growth factor, and vascular endothelial growth factor.[56] It is noteworthy that expression of the receptor for LDLox on BPH cells was increased more than 3 orders of magnitude by the pretreatment with TNF-α, suggesting that the metabolic inflammatory effect could have the potential to be greatly magnified by the concomitant presence of different inflammatory stimuli, such as infectious agents.

EFFICACY OF STATINS IN BPH: EVIDENCE FROM CLINICAL STUDIES

Evidence of the effect of hypolipidemic drugs on BPH is scanty and contradictory. A baseline evaluation of 6655 men recruited in the REDUCE trial showed less chronic inflammation on prostate biopsy in patients taking statins.[57] In the Olmsted County Study of Urinary Symptoms and Health Status Among Men, among 2447 community-dwelling men age 40−79 years followed up for a median of 13.8 years, those taking statins had significantly lower rates of BPE, urinary flow impairment, and moderate/severe LUTS, which translated into a 6.5- to 7-year delay in the onset of urinary complications compared with non-statin users.[58] A protective role of statins was also suggested by the cross-sectional results of the Boston Community Area Health Survey, which showed a significantly lower prevalence of LUTS in older men (age >60 years) treated with statins, but not in women or younger men treated with statins.[59] Contrasting results were reported by the Health Professionals Follow-Up

Study, a prospective study involving 51,529 male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians in the United States, which found an association between statin use and a modestly increased risk of LUTS development or progression.[60] However, there was no difference in the risk of LUTS between statin users and patients taking other medications for metabolic disorders, such as antihypertensive drugs,[60] suggesting that a medication-specific risk is unlikely and that the positive association is more likely the effect of a selection of subjects with worse metabolic conditions. A lack of association between statin use and incidence of LUTS was found in 2 Japanese studies conducted using large healthcare databases.[61,62] Strong biases should be recognized for both studies, however. In fact, the former was performed on a database collecting LUTS from reports of adverse events due to medication,[61] whereas in the latter, the incidence of LUTS was assumed from the new prescription of anticholinergic medications, such as solifenacin, imidafenacin, tolterodine, propiverine, flavoxate, and oxybutynin, which are mostly prescribed for storage LUTS not specifically associated with BPH.[62]

The role of statins in improving BPH/LUTS has been specifically assessed in several clinical trials. In a placebo-controlled randomized controlled trial (RCT), 350 men with LUTS and BPE and with a low-density lipoprotein (LDL) cholesterol level of 100−190 mg/dL were assigned at random to receive atorvastatin 80 mg/day or placebo.[63] After 6 months of treatment, no significant changes in prostate volume, urinary flow, or LUTS symptoms were found. Similarly, in a later small, nonrandomized clinical trial that included 37 men with BPH and LUTS treated with finasteride 5 mg/day and with lovastatin 80 mg/day if LDL cholesterol was >100 mg/dL, there were no differences between the statin-treated and untreated groups over a 4-month period.[64] A more recent RCT[65] including 137 men age >60 years with BPH and MetS assigned at random to receive simvastatin 40 mg, atorvastatin 20 mg, or placebo daily for 12 months reached a different conclusion. In that RCT, both study arms treated with statins showed a significant improvement in LUTS and a significant decrease in prostate volume, as assessed by transabdominal ultrasound.[65] In particular, the decrease in prostate volume, which was significantly greater in dyslipidemic men, was associated with the decrease in total cholesterol and the increase in HDL cholesterol.[65]

LOW T AND BPH

As noted above, the androgen dependence of prostate growth, although clear and well documented in early life, is a matter of debate for middle-aged and elderly men, who exhibit a progressive decline in T levels. The finding of no difference in intraprostatic androgen concentration between men with BPH and those without BPH[14] is further evidence that BPE is driven by factors other than androgens. As discussed above, chronic inflammation is a key element in the induction and progression of BPE, and there is evidence indicating that both infectious and metabolic agents, particularly dyslipidemia, can trigger this process. Despite current evidence suggesting that higher T is likely not involved in BPH development, this does not exclude the possibility of a role for this hormone in the pathogenic process. In fact, low, rather than high, T appears to be a risk factor for BPH and LUTS. In a spinoff study of the PCPT, lower total T and total T:17β-diol-glucuronide (a DHT metabolite) at baseline were associated with an increased risk of new occurrence of BPH over 7 years of follow-up.[66] In the Rancho Bernardo study, among 158 community-dwelling men who completed more than 20 years of follow-up, a lower baseline T:DHT ratio predicted the occurrence of clinically relevant LUTS.[67] Similarly, the Florey Adelaide Male Ageing Study, a population-based study involving 780 men age 35−80 years and followed for 5 years, identified lower baseline T as among the predictors for worsening in voiding LUTS.[68]

The mechanism by which low T could favor the development of BPH remains incompletely known; however, a role of T as a modulator of the inflammatory and immune responses within prostate tissue has been postulated.

ROLE OF ANDROGENS IN PROSTATIC INFLAMMATION: PRECLINICAL STUDIES

T has been demonstrated to have several effects on the immune system, including a decrease in TLR-4 expression by macrophages and their reduced synthesis of TNF and nitric oxide, increases in IL-10 and transforming growth factor β, and decreases in leukotriene and extracellular signal-regulated kinase synthesis by neutrophils.[69] Overall, these functions indicate an immunosuppressive effect of T. Accordingly, after a viral infection, orchiectomized rats have higher macrophage, $CD4^+$ T cell, and $CD8^+$ T cell counts than intact animals.[70,71] Moreover, it has been demonstrated that T treatment can increase the susceptibility to endotoxic shock in orchiectomized rats.[72] The immunomodulatory effect of T treatment also has been shown in experimental models of several inflammatory and autoimmune diseases, such as autoimmune orchitis,[73] arthritis,[74] cholangitis,[75] autoimmune encephalomyelitis,[76] and renal ischemia-reperfusion injury.[77] Similarly, our group has found an anti-inflammatory effect of T in the prostate. In human prostate stromal cells isolated from patients with BPH, treatment in vitro with different proinflammatory stimuli, such as TNF-α or lipopolysaccharide, or coculturing with activated $CD4^+$ lymphocytes, are able to significantly enhance the secretion of several cytokines and growth factors.[39] The pretreatment of BPH stromal cells with DHT significantly blunts the release of these cytokines and growth factors in a dose-dependent fashion.[39] In addition, in stromal BPH cells, DHT was able to inhibit the TNF-α-induced translocation of NF-kB p65 from cytoplasm to the nucleus.[9] Along with reducing their own production of proinflammatory cytokines, DHT-treated stromal BPH cells were also able to affect the activated $CD4^+$ lymphocytes by inhibiting their proliferation.[39]

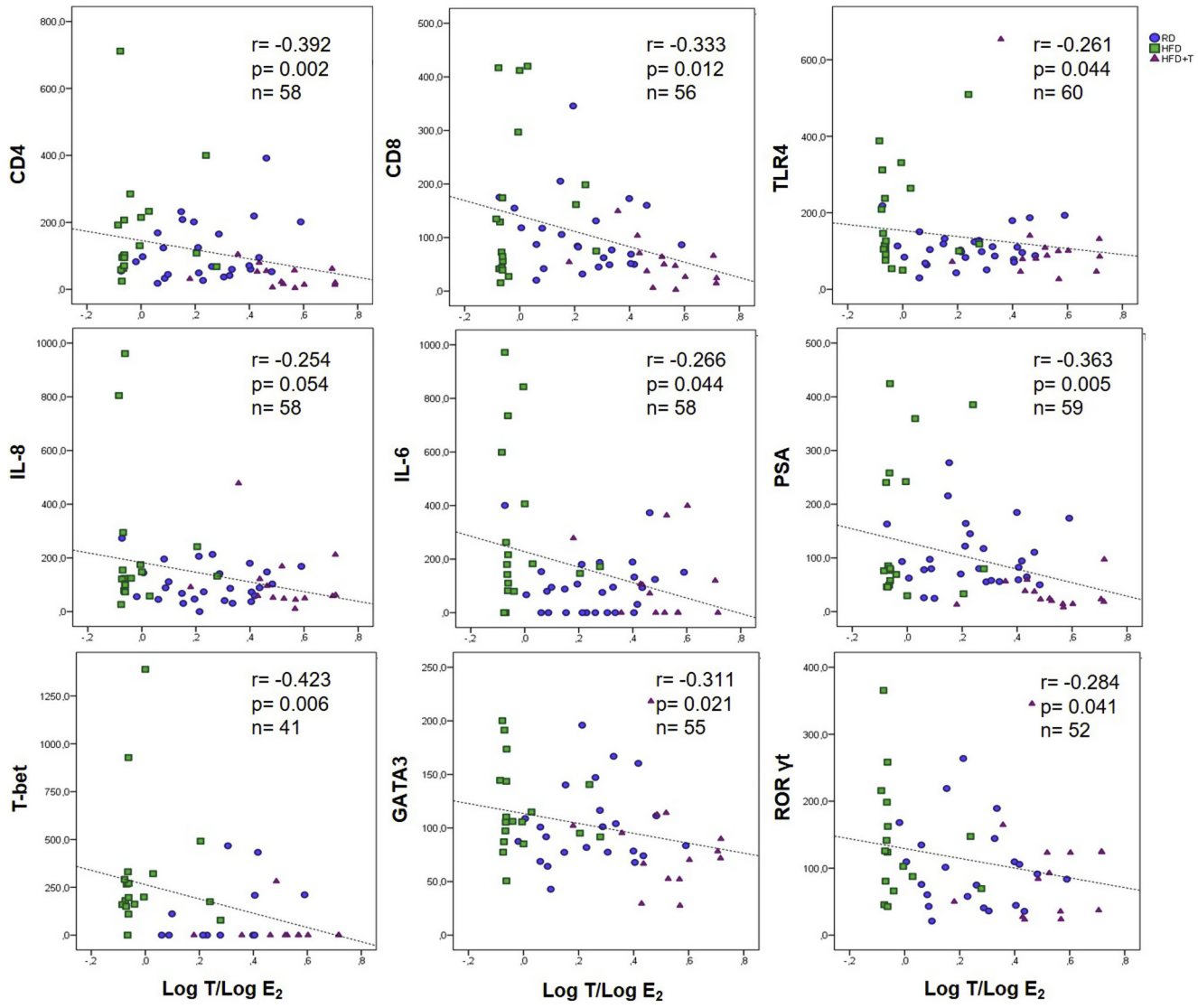

Figure 1. Association between testosterone:estradiol (T:E_2) ratio and expression of several inflammation-related genes in the prostate of rabbits fed a regular diet (RD) or a high-fat diet (HFD) without or with cotreatment with T (HFD + T) for 12 weeks. The T:E_2 ratio is expressed as the ratio between the log-transformed values (log T/log E_2). Gene expression was performed by quantitative reverse-transcription polymerase chain reaction analysis in the animal's prostate samples and are plotted on the *y*-axis as the mRNA expression level reported as an arbitrary unit. The statistics in each panel are derived from univariate analysis and reported as Spearman's coefficient with the level of significance.

Interestingly, DHT had similar effects when given in vitro to BPH cells whose proinflammatory secretion profile was stimulated by metabolic triggers, such as LDLox or insulin.[56] This raises the question of whether androgens may play a role in the relationship between MetS and BPH. In fact, it is now well known that hypogonadism is a frequent finding in men with MetS ,with a prevalence ranging between 15% and 45% depending on the definition used and the population studied.[78] In the aforementioned rabbit model of MetS, besides the metabolic derangements, HFD induces an overt hypogonadism characterized by organic features of androgen deficiency, low serum T, and hyperestrogenism.[52,54] In this experimental model, HFD-induced MetS was also associated with significantly increased expression of *AR, ERα, ERβ*, and *GPR30/GPER* in the prostate,[54] thus suggesting an increased responsiveness to sex hormones. Accordingly, treating HFD rabbits with T for 12 weeks was able to prevent in the prostate the proinflammatory modifications in gene expression and the development of inflammatory infiltrate and fibrosis which was induced by HFD (see above).[54] Conversely, treatment with tamoxifen, which in the rabbit prostate acts as a GPR30/GPER agonist, rather than an ER agonist,[19] did not prevent—and even magnified—the inflammatory features in the prostate of HFD rabbits.[19] Thus, MetS-related inflammation in the prostate is a function not only of lower T levels, but also of higher estrogen levels. Figure 1 shows the relationship between the T:E_2 ratio and the expression levels of several genes in the prostate. When considering rabbits fed for 12 weeks with a regular diet or an HFD with or

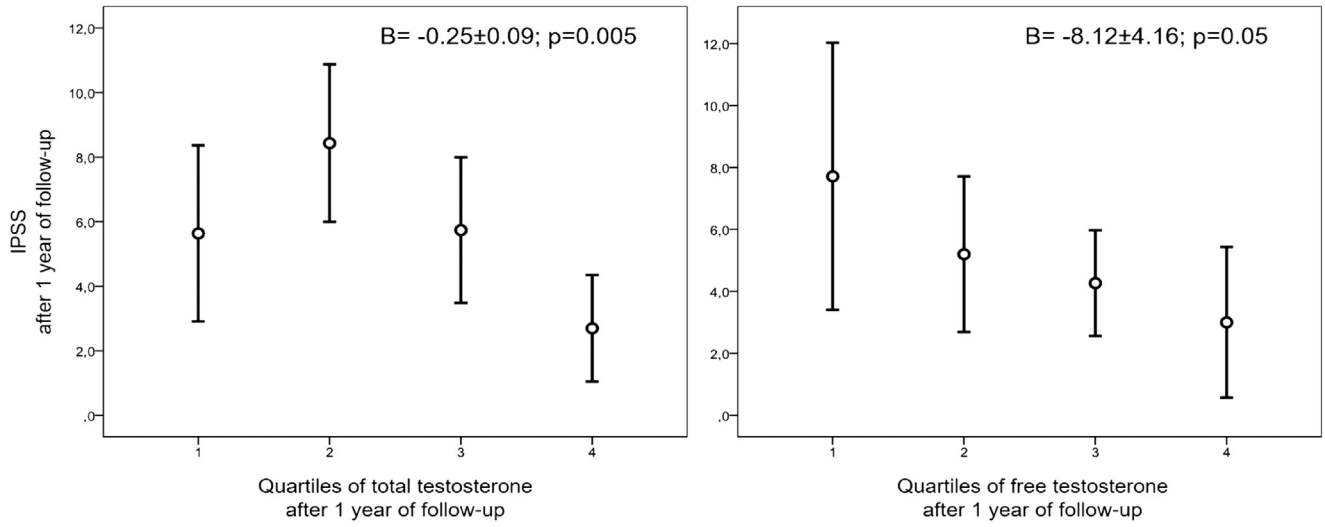

Figure 2. Relationship between total or free testosterone (T) and the International Prostate Symptom Score (IPSS) after 1 year of follow-up in the SIAMO-NOI registry [86]. Data are derived from 80 hypogonadal men who started treatment for hypogonadism after recruitment and 55 men who remained untreated for the entire 1-year observation period. The statistics reported in each panel are derived by linear regressions with the IPSS after 1 year of follow-up as the dependent variable and total or free T at the same visit as the independent variable. The data are adjusted for age, baseline IPSS, and baseline T (total or free, as appropriate).

without cotreatment with T, a lower T:E_2 ratio was associated with increased expression of a number of cytokines and markers of activation of cells involved in the immune response, thus suggesting that relative hypogonadism and hyperestrogenism favor a proinflammatory milieu.

EFFECT OF T THERAPY ON BPH AND LUTS: EVIDENCE FROM OBSERVATIONAL STUDIES

The evidence we report here contrasts with the historical view that T therapy (TTh) is detrimental for the prostate and should be avoided in men with BPH and LUTS. This belief is based mainly on the studies reported in the 1940s by Huggins and Hodges, who observed in a limited number of men with metastatic prostate cancer that castration resulted in cancer regression, whereas T administration in 1 patient was followed by an increase in cancer extension.[79] Clinical trials assessing the effect of TTh on BPH and LUTS are reassuring, however. A small pilot study involving 30 men treated with T gel 50 mg daily or T undecanoate 1000 mg for 3–6 months showed a beneficial effect of TTh on LUTS in hypogonadal men.[80] In a later observational trial, 117 hypogonadal men with a mean age of 59.5 ± 6.0 years treated with injectable T undecanoate 1000 mg for 12 weeks showed progressive improvement in LUTS, as assessed by the International Prostate Symptoms Score (IPSS), and a decrease in residual urinary volume, with no change in prostate size.[81] This study was extended with a larger sample (n = 656 men) and a longer follow-up (median 8 years), which substantially confirm the previous results and demonstrated sustained improvements in LUTS and postvoiding urinary volume in men receiving T undecanoate.[82,83] A comparable improvement in IPSS was reported in an observation of 261 hypogonadal men of comparable age treated with injectable T undecanoate for 5 years.[84] The Registry of Hypogonadism in Men (RHYME), a multinational registry of hypogonadal men with a follow-up of 3 years aimed primarily at assessing prostate cancer outcomes after TTh treatment, involved 999 subjects with an average age of 59.1 ± 10.5 years, of whom 75% were treated for hypogonadism and the remaining 25% remained untreated.[85] During follow-up, the men treated with TTh demonstrated improved LUTS, achieving a 7%–8% lower IPSS compared with the untreated patients.[85] In the SIAMO-NOI registry, which collected data on 432 hypogonadal men treated in 15 Italian andrologic centers (mean age 50.9 ± 14.9 years), a significant improvement in LUTS over 1 year of follow-up was found among 80 men who started TTh compared with 55 men who remained untreated for the entire observation period.[86] Figure 2 shows the relationship between IPSS and total or free T levels after 1 year of follow-up in hypogonadal men involved in the SIAMO-NOI registry who started androgen therapy or remained untreated during the observation period. After adjusting for age and baseline T and IPSS, higher total and free T were associated with lower IPSS, indicating a T-dependent improvement in LUTS. In contrast, it should be mentioned that a small observational study including 20 obese hypogonadal men with LUTS failed to show any differences in LUTS, urinary flow parameters, or prostate size between men treated for 60 months with T undecanoate and those who remained untreated.[87]

EFFECT OF T THERAPY ON BPH AND LUTS: EVIDENCE FROM INTERVENTIONAL TRIALS

Results from RCTs are less geared toward improvements in LUTS associated with TTh and mostly suggest a null effect, but

none of these studies found a worsening. These results were recently subjected to a meta-analysis of 14 RCTs with a total of 2029 men (mean age 64.5 years) with late-onset hypogonadism followed for a mean of 34.4 months.[88] Neither TTh nor placebo was associated with any significant change in LUTS, even though a slight, albeit significant, improvement was found when considering only RCTs that used injectable T formulations.[88]

To date, only a few RCTs have evaluated the effects of TTh on objective measures of prostate health, such as prostate volume, urodynamic data, and tissue inflammation. A small RCT of healthy community-dwelling men did not find any differences in prostate size, as assessed by ultrasound, or in postvoiding urine volume between patients treated for 3 months with intramuscular T enanthate 100 mg weekly or placebo.[89] A 12% increase in prostate volume over 8 months of TTh with oral T undecanoate 160 mg daily was found in another placebo-controlled RCT involving 25 middle-aged men; however, that study found no change in the urodynamic parameters associated with TTh.[90] In an RCT of 25 men with late-onset hypogonadism, T gel 50−100 mg daily for 1 year resulted in improvements in several parameters of cystometry and pressure-flow analysis, including bladder capacity and compliance as well as detrusor pressure at maximal flow, accompanied by a significant reduction in IPSS.[91] Significant improvements in maximum flow and voiding volume associated with TTh was also found in an open-label RCT of 46 hypogonadal men with BPH assigned at random to receive injectable T enanthate 250 mg every 4 weeks or remain untreated.[92] Marks et al[93] reported data on prostate tissue from 40 hypogonadal men treated for 6 months with placebo or T enanthate 150 mg i.m. every 2 weeks. Although serum hormone levels normalized in the TTh arm, no or few effects were found in terms of intraprostatic androgen levels, expression of androgen-dependent genes or genes related to cell survival or angiogenesis in prostate tissue, LUTS, or urodynamic parameters.[93] In recently reported preliminary data from a RCT of 120 men with MetS ad BPH, T gel 5 g/day administered for 6 months to hypogonadal men was associated with a moderate improvement in LUTS, despite a significant increase in prostate size compared with men receiving placebo.[94] More importantly, TTh was associated with a significant decline in prostate artery flow velocity and acceleration, as assessed by transrectal color Doppler ultrasound, and with decreased expression of inflammation-related genes, such as *cyclooxygenase-2, MCP1*, and *RORγt*.[94]

Taken together, these results are reassuring concerning the role of T in prostate health, depicting it as a friend rather than a foe, even in men with BPH and LUTS. The apparent contradiction of these results with the success of 5-alpha reductase inhibitors in treating LUTS merits closer investigation. Undoubtedly, treatment with 5-alpha reductase inhibitors results in a prostate volume decrease, which in turn translates into an improvement in LUTS. Nonetheless, it should be kept in mind that studies assessing intraprostatic androgen levels have linked 5-alpha reductase inhibition with a decrease in DHT and an increase in T.[95] Conversely, the mutual proportion of intraprostatic T and DHT do not appear to be affected by TTh.[93] Increased intraprostatic T:DHT ratio could provide more substrate for conversion into estrogens, and this could further support prostate inflammation. Accordingly, results from the PCPT show a higher grade of prostate inflammation in men treated with 5-alpha reductase inhibitors compared with those receiving placebo.[96] Thus, it can be hypothesized that TTh and 5-alpha reductase inhibitors have effects on different aspects of BPH. Support for this hypothesis, as well as the long-term consequences of these 2 different mechanisms, must be provided by specific studies.

CONCLUSION: A JOINT HYPOTHESIS FOR PATHOGENESIS OF BPH

The pathogenesis of BPH remains incompletely understood. Inflammation is a key aspect of this process; however, how this mechanism is initiated is a subject for further research. Along with infectious agents, metabolic stimuli, such as dyslipidemia, are emerging as pivotal elements in the development of prostatic enlargement. MetS is often accompanied by low T and a relative hyperestrogenism. Mounting evidence shows that low, rather than high, T levels favor prostate inflammation and that hyperestrogenism also may play a role. Considering all these data, we postulate that BPH results from the actions of multiple factors occurring together or at different time points, which can reinforce and favor their mutual detrimental effects. The initial steps in this process are likely to occur early in life with an overt or subclinical prostatitis, probably influenced by infectious agents. The resulting prostatic inflammation could be amplified and maintained by metabolic derangements occurring in such conditions as MetS. Low T and the relative hyperestrogenism secondary to MetS could further exacerbate the immune process, leading to a chronic inflammation. When prostatitis becomes chronic, a number of cytokines are produced that act in the tissue to maintain the pathological condition. On the other hand, several growth factors are secreted, and their elevated concentrations lead to prostate remodeling and enlargement. The resulting mechanical obstruction and inflammatory damage are the basis of BPH and its associated urinary symptoms.

This hypothesis, based on existing experimental evidence, remains to be proven with ad hoc intervention studies. However, if verified, it carries the important message that BPH can be limited or even avoided by controlling very common modifiable risk factors, such as dyslipidemia, obesity, and insulin resistance. In addition, treating hypogonadism, which frequently accompanies MetS, not only is not detrimental for the prostate, but also could even be a therapeutic resource for relieving urinary symptoms and limiting the inflammatory process in the prostate.

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Conflicts of interest: The authors report no conflicts of interest.

Funding: None.

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