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INVITED OPINION

Male Aging

Testosterone therapy: a friend or a foe for the aging men with benign prostatic hyperplasia?

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One of the major concerns for the prescription of medications containing testosterone (T) in the aging men with T deficiency (TD) is prostate disorders (such as benign prostatic hyperplasia, BPH) and their related symptoms (lower urinary tract symptoms, LUTS). This is because prostate is an androgen-responsive gland; however, the androgen dependence of prostate growth, well demonstrated in earlier phases of life, has no clear evidence in late adulthood and senescence. In fact, after the age of 40 years, BPH becomes increasingly more prevalent. On the other hand, in men older than 40 year, a progressive decline in T is observed. These epidemiological data are a starting point for questioning a putative detrimental role of T on the prostate health in the ageing man.

In addition, even the administration of supraphysiological doses of T in adult healthy men with or without dutasteride did not result in a significant change in prostate volume over 20 weeks of treatment.[1] Based on this evidence, it is not surprising that epidemiological studies failed to demonstrate that BPH is associated with higher serum T.[2] Conversely, there is even an evidence of a negative relationship between T and BPH. In a derivative study of the Prostate Cancer Prevention Trial, involving 1417 men free from BPH, lower total T at baseline predicted the occurrence of BPH over 7 years of follow-up.[3] Similarly, low T was found as a predictor of worsening in LUTS in the Florey Adelaide Male Ageing Study and in the Rancho Bernardo Study, lasting 5 years and 20 years, respectively.[4,5]

TD in midlife and senescence is a relatively common finding, with a prevalence of about 15% in the general population.[6] Metabolic conditions included in the construct of metabolic syndrome (MetS) are common causes of TD in adulthood, and, among men with MetS, the prevalence of low T is at least doubled.[6] Interestingly, in men with MetS, the prevalence of BPH is also increased.[7] Evidence from epidemiological studies of a mutual association among MetS, low T, and BPH is a sound basis for hypothesizing that these three conditions are part of a single clinical picture. Amounting evidence in support to this hypothesis is provided by experimental preclinical studies.

It is important to underline that, before being a hyperplastic condition, BPH is an inflammatory disease with peculiar features. Within prostate tissue, consequent to proinflammatory stimuli whose nature is still only partially known, a progressive shift from acute to chronic histopathological characteristics of inflammation is documented. Prostatic chronic inflammation occurring in BPH is characterized by the secretion of interleukins (IL), such as IL-4, IL-13, IL-17, and IL-15, typical of a Th2 or Th17 immune response.[7] In addition, besides specialized immunocompetent cells, prostatic stromal cells have the potential to become antigen-presenting cells (APC), and, accordingly, it has been demonstrated that they are able to activate $CD4^+$ T lymphocytes.[7] In turn, the activated lymphocytes secrete cytokines and growth factors, which self-maintain the inflammatory process and favor the proliferation of stromal cells leading to BPH.[7]

This peculiar pattern of secretion and mutual stimulation by lymphocytes and stromal BPH cells is demonstrated by *in vitro* studies using conventional inflammatory stimuli, such as lipopolysaccharide or tumor necrosis factor-alpha (TNF-alpha).[8] However, similar responses are produced by stimulating stromal BPH cells with oxidized low-density lipoproteins (oxLDL).[9] This is an interesting finding, because it could provide a possible link to explain the epidemiological association between MetS and BPH. In fact, observational clinical studies have pointed out that, among the components of MetS, dyslipidemia is most strongly associated with the extent of inflammation. This has been found in patients who have an overt and advanced prostatic disease. In prostatic tissue samples from 244 men undergoing surgery for BPH, the histopathologic inflammatory score was increasingly higher as the number of components of MetS increased, with the strongest association documented for hypertriglyceridemia and lower high-density lipoprotein (HDL) cholesterol.[9] Interestingly, the relationship between dyslipidemia and prostatic inflammation has been observed also in younger men without an overt BPH. In a population of men undergoing a medical consultation for couple infertility, a greater prostate volume, as assessed by transrectal ultrasound, was associated with lower HDL cholesterol.[10]

In this context, a rabbit model of MetS induced by a high-fat diet (HFD) represents a useful experimental tool for the investigation of the causative role of MetS on BPH. In HFD animals, prostate was characterized by histopathological features of inflammation, fibrosis, and hypoxia, resembling the characteristics of BPH observed in humans.[11] Interestingly, **Figure 1**, expanding previously reported data,[12] shows that, in rabbit prostate, the gene expression of markers of inflammation is higher as cholesterol levels increase. It is noteworthy that, in HFD

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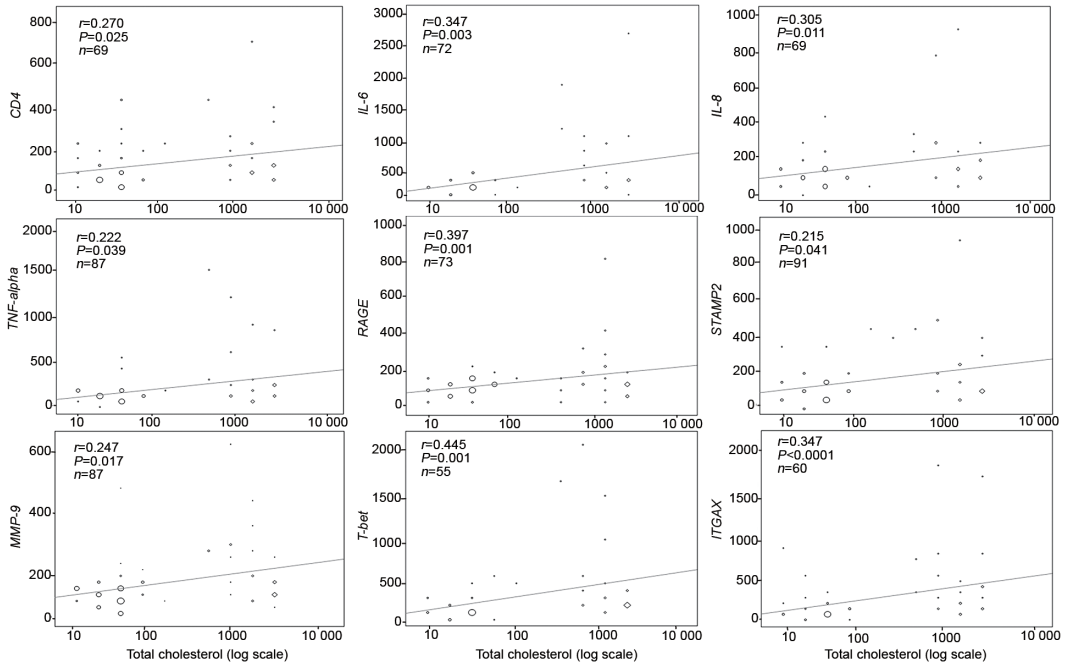

Figure 1: Association between total cholesterol (log scale) and expression of several inflammation-related genes in the prostate of rabbits fed for 12 weeks a RD (open circles) or a HFD (open diamonds). Gene expression was performed by quantitative RT-PCR analysis in the prostate samples of the aforementioned experimental animals and calculated according to comparative C_t method by rRNA subunit 18S as the reference gene for normalization. Results in the Y-axis are reported as the level of mRNA expression in percentage over the mean value of the RD group. Statistics in each panel are derived from univariate analysis and reported as Spearman's coefficient with the level of significance and number of experimental animals. RD: regular diet; HFD: high-fat diet; RT-PCR: real-time polymerase chain reaction; rRNA: ribosomal ribonucleic acid; *CD4*+: cluster of differentiation 4; *IL-6*: interleukin 6; *IL-8*: interleukin 8; *TNF-alpha*: tumor necrosis factor-α; *RAGE*: receptor for advanced glycation end products; *STAMP2*: six transmembrane protein of prostate 2; *MMP-9*: matrix metallopeptidase 9; *T-bet*: T-box transcription factor; *ITGAX*: integrin alpha X.

rabbits, besides MetS, hypogonadotropic hypogonadism occurs and that T treatment is able to prevent the development of the previously mentioned histopathological features reminiscent of BPH,[11] as well as the expression of most markers of inflammation (**Figure 2**), thus confirming previous data on a smaller sample.[12]

The anti-inflammatory role of T treatment in HFD rabbits finds an explanation in the emerging immunomodulatory functions of T. In macrophages, T demonstrated to decrease the expression of toll-like receptor 4, as well as the secretion of TNF-alpha and nitric oxide, and, in neutrophils, to increase the production of IL-10 and transforming growth factor β with a decrease of leukotriene synthesis.[13] Consistent with these immunosuppressive effects, in human stromal BPH cells, the *in vitro* treatment with dihydrotestosterone (DHT) is able to reduce the cytokine secretion induced by proinflammatory stimuli, including oxLDL and insulin.[9]

These experimental data suggest that T is a friend, rather than a foe, for prostate health even in BPH conditions. However, it should be noted that opposite evidence supporting an adverse effect of T on the prostate and LUTS is present. In an experimental rat model, the treatment with DHT with or without estradiol was able to induce a significant increase of prostate volume and decrease of urine volume voided as compared with controls.[14] In addition, the clinical success in improving LUTS of the 5α-reductase inhibitors (5ARIs), which decrease circulating and intraprostatic DHT levels, is well proven by clinical trials.[15,16] Nonetheless, this does not contrast with the aforementioned beneficial role of T on the prostate. Indeed, 5ARIs decrease prostate volume,[15,16] but they have been associated with an increased grade of prostatic inflammation, as compared with placebo,[17] further suggesting the anti-inflammatory role of T. Hence, it is conceivable that the androgen deprivation and the androgen supplementation may act on LUTS by different mechanisms, the former reducing the prostate volume and the latter modulating the inflammatory process.

Supporting evidence from clinical studies for a beneficial role of T on the prostate is still circumstantial. Observational longitudinal studies evaluating prostatic outcomes almost consistently found an improvement in LUTS and residual urinary volume, without any significant change in prostate volume.[18] However, it is important to underline that these studies often involve small samples observed for short follow-up periods. In addition, they usually employ less standardized protocols of data collection, and, even more importantly, the assignment to the treated or untreated arms is arbitrary rather than randomized, thus possibly resulting in allocation bias.

Although randomized clinical trials (RCT) did not provide such enthusiastic results, it should be noted that none of these found any worsening in LUTS, as recently shown by a meta-analysis of 14 RCTs including overall 2029 men with TD with borderline-low T levels[19] and further confirmed by a more recent meta-analysis evaluating studies, which enrolled only men with unequivocally low serum T.[20] Besides the assessment of subjective outcomes, only a few RCTs evaluated objective prostatic parameters in TD men treated with T. In particular, data on the effect of T therapy (TTh) on prostatic inflammation are lacking. Recently, preliminary data from a RCT, including 120 men with MetS and BPH, showed that a 6-month treatment with T gel 5 g daily, administered to hypogonadal men, is able to improve ultrasound markers of prostatic inflammation as well as the expression of inflammation-related genes, such as cyclooxygenase-2, monocyte chemoattractant protein 1 (*MCP1*), and related orphan receptor gamma-t (*RORγt*).[21]

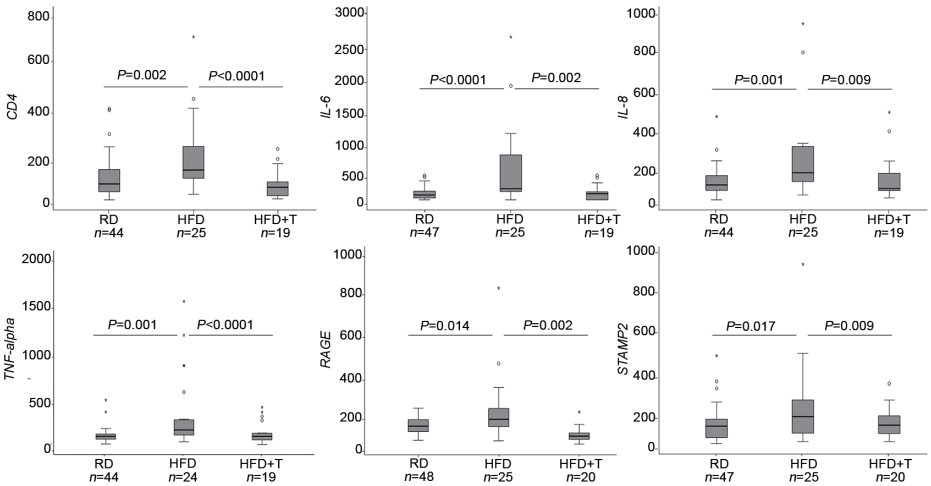

Figure 2: Expression in the prostate of inflammatory genes according to three experimental groups: rabbits fed for 12 weeks a RD or a HFD with or without a cotreatment with injectable testosterone (HFD+T). Relative mRNA expression of inflammatory markers was evaluated using quantitative RT-PCR. Data were calculated according to comparative C_t method by rRNA subunit 18S as the reference gene for normalization. Results are expressed in percentage over the mean value of the RD group and are reported as median (interquartile range), 95% confidence intervals with °denoting outliers and *extreme observations. Statistics in each panel is derived from Mann–Whitney U-test. RD: regular diet; HFD: high-fat diet; HFD+T: high-fat diet + testosterone; RT-PCR: real-time polymerase chain reaction; rRNA: ribosomal ribonucleic acid; *CD4*: cluster of differentiation 4; *IL-6*: interleukin 6; *IL-8*: interleukin 8; *TNF-alpha*: tumor necrosis factor-alpha; *RAGE*: receptor for advanced glycation end products; *STAMP2*: six transmembrane protein of prostate 2.

According to the available evidence, the concerns on the use of TTh in men with BPH and LUTS have no supportive experimental basis. BPH can be considered part of the constellation of derangements occurring in MetS. TD associated with MetS has the potential to exacerbate prostatic inflammation, thus favoring its progression to BPH. In this view, TTh could represent an obvious solution to improve the prostatic inflammation occurring in MetS. Although specifically designed RCTs are needed, it is likely that, in the next future, we will assist to a transition of TTh from the side of the enemies of the prostate to that of the allies.

AUTHOR CONTRIBUTIONS

GR and MM conceived the article and designed the methodology; GR and LV collected the data; GR drafted the article; GR, LV, and MM revised and edited the final article. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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