Casual Friday Series

# Functional Approaches to Prostate Health

A Biogenetix Clinical Presentation

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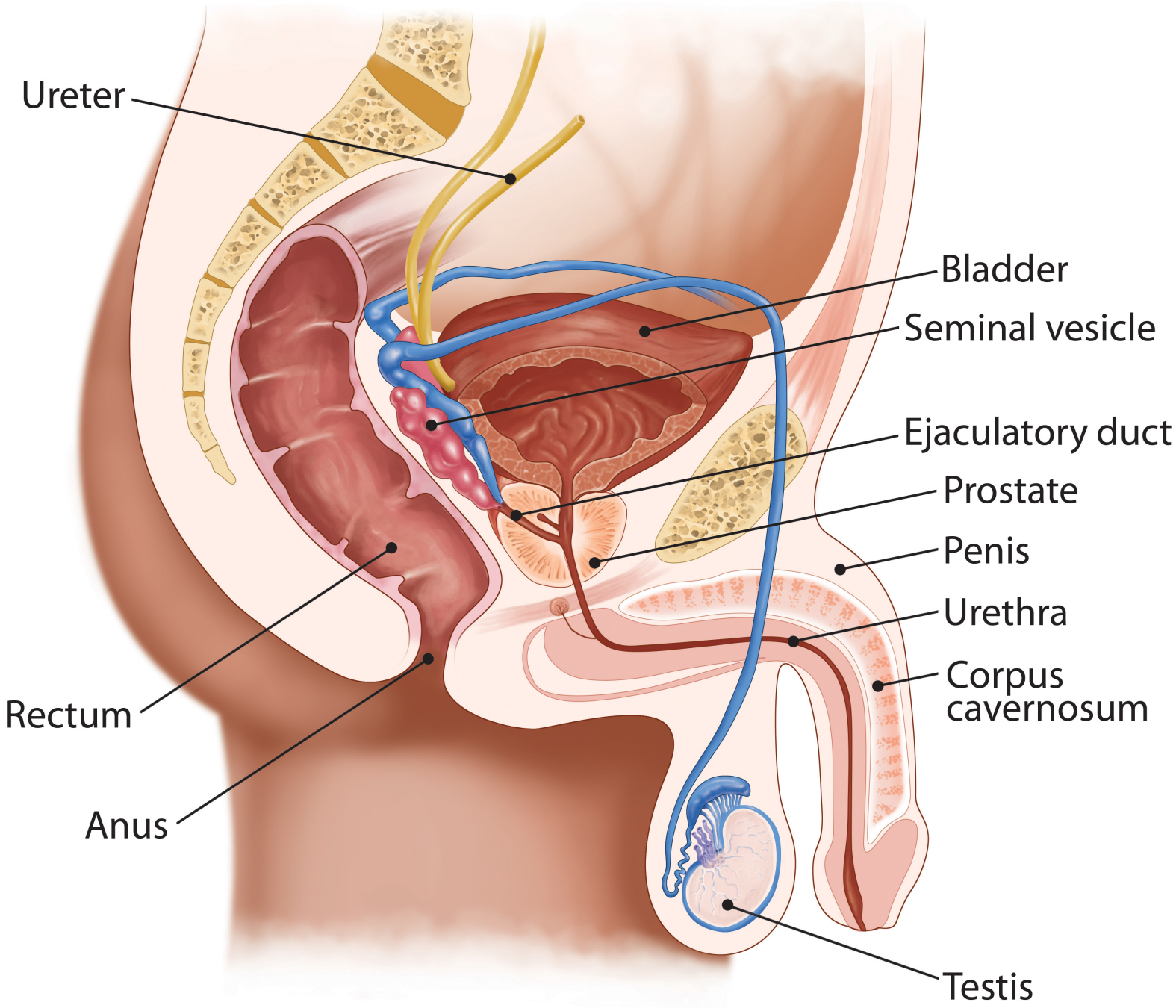
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*




https://www.prostateconditions.org/images/iStock-176986341.jpg

Complications of an enlarged prostate can include:

•**Sudden inability to urinate (urinary retention).** You might need to have a tube (catheter) inserted into your bladder to drain the urine. Some men with an enlarged prostate need surgery to relieve urinary retention.

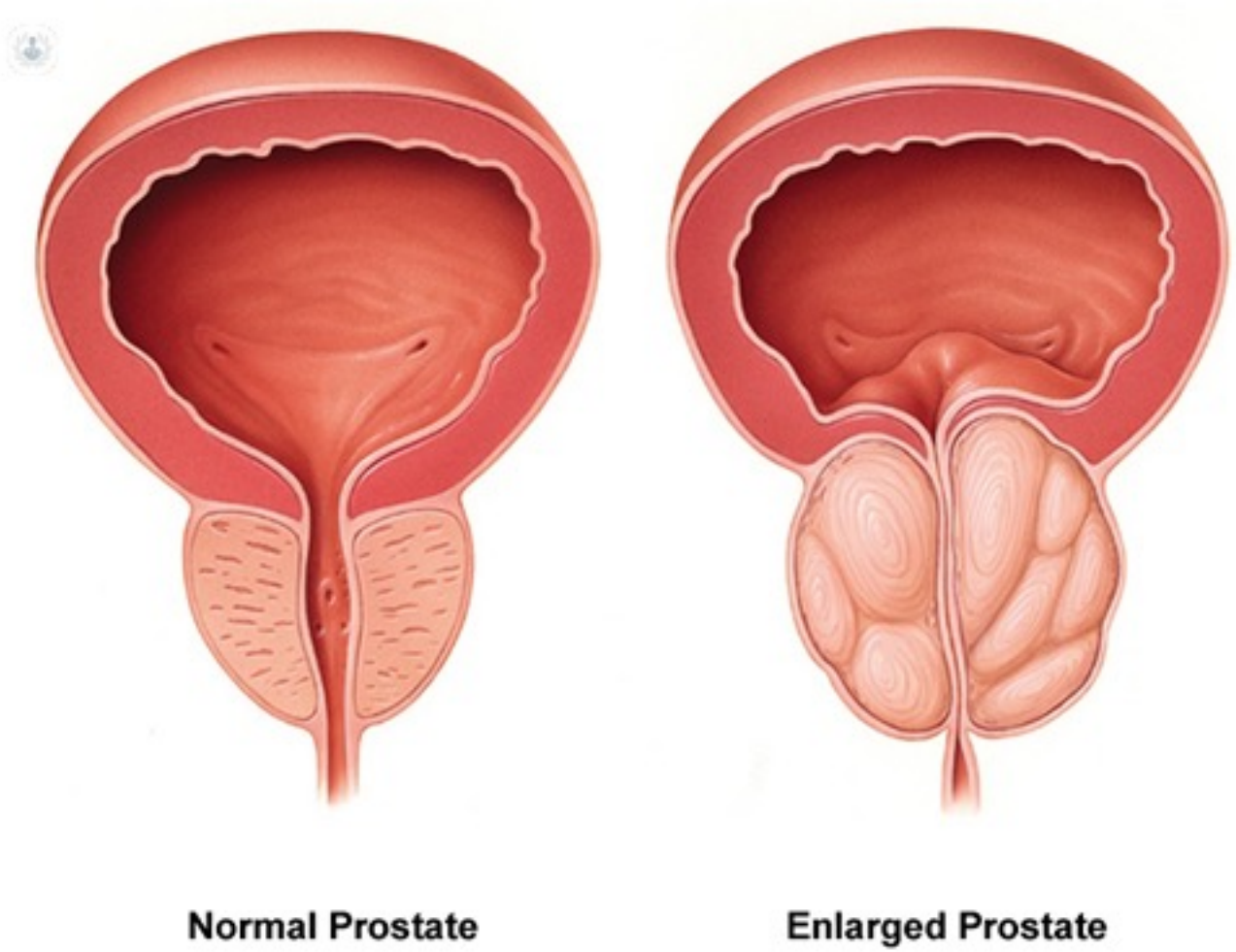
•**Urinary tract infections (UTIs).** Inability to fully empty the bladder can increase the risk of infection in your urinary tract. If UTIs occur frequently, you might need surgery to remove part of the prostate.

•**Bladder stones.** These are generally caused by an inability to completely empty the bladder. Bladder stones can cause infection, bladder irritation, blood in the urine and obstruction of urine flow.

•**Bladder damage.** A bladder that hasn't emptied completely can stretch and weaken over time. As a result, the muscular wall of the bladder no longer contracts properly, making it harder to fully empty your bladder.

•**Kidney damage.** Pressure in the bladder from urinary retention can directly damage the kidneys or allow bladder infections to reach the kidneys.

https://www.mayoclinic.org/diseases-conditions/benign-prostatic-hyperplasia/symptoms-causes/syc-20370087



Normal Prostate

Enlarged Prostate

https://www.topdoctors.co.uk/files/Image/large/5a9432cf-7a0c-4eaa-b1d3-0fd825bbab96.jpg

The Inventor of PSA Testing:

https://www.medscape.com/viewarticle/828854

**REVIEW article**

Front. Endocrinol., 22 February 2021 | https://doi.org/10.3389/fendo.2021.554078

# Endocrinology of the Aging Prostate: Current Concepts





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Benign prostate hyperplasia (BPH), one of the most common diseases in older men, adversely affects quality-of-life due to the presence of low urinary tract symptoms (LUTS). Numerous data support the presence of an association between BPH-related LUTS (BPH-LUTS) and metabolic syndrome (MetS). Whether hormonal changes occurring in MetS play a role in the pathogenesis of BPH-LUTS is a debated issue. Therefore, this article aimed to systematically review the impact of hormonal changes that occur during aging on the prostate, including the role of sex hormones, insulin-like growth factor 1, thyroid hormones, and insulin. The possible explanatory mechanisms of the association between BPH-LUTS and MetS are also discussed. In particular, the presence of a male polycystic ovarian syndrome (PCOS)-equivalent may represent a possible hypothesis to support this link. Male PCOS-equivalent has been defined as an endocrine syndrome with a metabolic background, which predisposes to the development of type II diabetes mellitus, cardiovascular diseases, prostate cancer, BPH and prostatitis in old age. Its early identification would help prevent the onset of these long-term complications.

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LUTS and BPH have long been considered a relative contraindication to testosterone replacement therapy (TRT). However, recent studies have contradicted the classic idea that androgens inevitably stimulate prostate growth (17). According to the saturation model, the prostate is sensitive to changes in androgen levels when they occur in a severe low range, but this sensitivity is lost for T levels corresponding to mild hypogonadism or eugonadal. Indeed, prostate ARs become saturated at relatively low T levels and thus, the gland becomes unresponsive to further increases in T levels (18). Experimental and clinical studies suggest that the saturation point for human prostate tissue probably occurs in the very low range of T levels, but a precise cutoff value has not been established; it could vary among men

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However, although current evidence suggests that higher T levels are not involved in BPH development, T seems to have a role in this pathogenic process by stimulating inflammation within prostate tissue. Inflammation has a crucial role in the pathogenesis of BPH and low, rather than high, T may stimulate prostate inflammation (12). Nevertheless, an anti-inflammatory effect of T in the prostate has also been described. In an experimental study using human prostatic stromal cell cultures, the treatment *in-vitro* with different pro-inflammatory stimuli, such as tumor necrosis factor α (TNF-α) or lipopolysaccharide (LPS), or co-culturing with activated CD4β lymphocytes, significantly enhanced the secretion of several cytokines and growth factors (24). The pre-treatment of BPH stromal cells with DHT inhibited

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the high-fat diet that appears to play a role in the development and even progression of BPH/LUTS (25). Interestingly, they found that MetS severity was associated with an increase of *AR* and *estrogen receptor* α (*ERα*), but not of *estrogen receptor β* (ER*β*) gene expression within the prostate (10). This suggests that the prostate could become more sensitive to sex hormone changes that occur during MetS. Indeed, TRT not only corrects the low T levels and the rise of estrogen levels which are typical of MetS, but it also normalizes the majority of MetS-induced prostate alterations (25).

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17ß-Estradiol ($E_2$) is considered the most potent estrogen in men and it mainly originates from aromatization of T in fat and muscle, whereas about 20% is secreted by Leydig cells (42). In aging men, paralleling the decrease of T levels, the ratio of estrogens to androgens shows an important increase (43). There are several endogenous and exogenous estrogens which may play an important role in prostate. Endogenous estrogens include estrone ($E_1$), which is considered to have minimal influence within the prostate, and estriol ($E_3$), the main estrogen of pregnancy, which is present in minimal concentrations in men. However, $E_2$ can be a potent inducer of prostatic proliferation (44). Local steroids with ER agonist activity include also 5α-androstane-3β, 17β-diol (3βAdiol), and 7α-hydroxy-DHEA (7HD). The effects of these sex steroids are not fully understood but they seem to influence prostate hyperplasia (44). Exogenous estrogens include therapeutic drugs, phytoestrogens, and endocrine disruptors. ERs have a high affinity for environmental estrogens such as bisphenol A (BPA), phthalates, pesticides, etc. In rodent studies, developmental BPA, DES, or $E_2$ exposure affects prostate epigenome and thus causes increased prostate susceptibility to dysplasia and hormonal carcinogenesis with aging (45).

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Recent studies suggest that not only low T levels, but also an increase of estrogens may favor BPH/LUTS progression (10). Marmorston and colleagues first reported that the $E_2$/T ratio in 24-h urinary collections was elevated in men with BPH compared to normal controls (49). Other epidemiologic studies have found an association between BPH and higher serum estrogen levels or estrogen/androgen ratio (50, 51). As previously reported, prostate inflammation could be amplified and maintained by metabolic alteration occurring in conditions such as MetS. Vignozzi and colleagues showed that HFD rabbits had higher $E_2$ to T ratio and lower urinary tract fibrosis, which improved with TRT (25). Recent evidence has also shown that leptin, a hormone produced by adipocytes, induces proliferative effects in prostate cells. This effect may be partially mediated by the direct effect of leptin on estrogen metabolism, as leptin induces aromatase expression (52).

Therefore, ERα, as a key mediator, is also a potential therapeutic target in BPH. The block of conversion of androgens to estrogens by aromatase inhibitors seems to prevent prostate hyperplasia (12). Similar to aromatase inhibitors, selective estrogen receptor modulators (SERMs) have shown anti-proliferative effects on prostate tissue (53).

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A recent retrospective study carried out in about 900 patients reported that, after correction for age, insulin levels and insulin-resistance are significantly associated with prostate volume. Interestingly, MetS predicted BPH/LUTS clinical progression (103), thus pointing to the additional role of MetS, other than insulin, in BPH/LUTS. A systematic review with meta-analysis performed on 8,476 participants, including 5,554 (30.1%) with and 12,922 (69.9%) without MetS showed a significantly higher prostate volume in patients compared to controls (104).

The National Cholesterol Education Program adult treatment panel III (2005 revision) defines MetS as the presence of three or more criteria among the following: i) abdominal obesity (waist circumference >102 cm), ii) hypertriglyceridemia (>150 mg/dl) or medications, iii) low high-density lipoprotein (HDL) cholesterol (<40 mg/dl) or medications, iv) hypertension (>130/85 mmHg) or medication, v) high fasting glucose (>110 mg/dl) or medication (105). The evidence supports an association between BPH and each of the MetS components (102).

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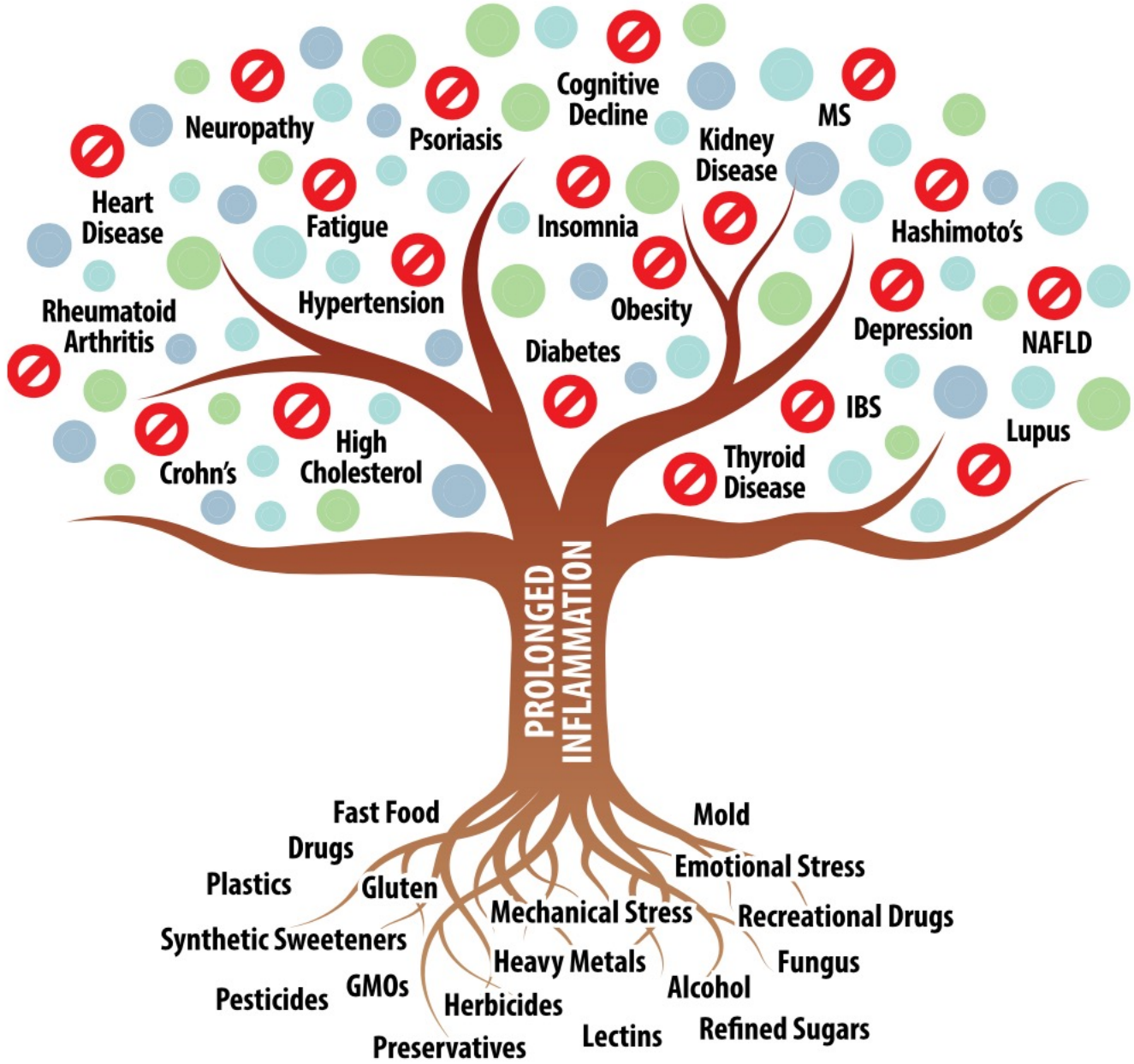
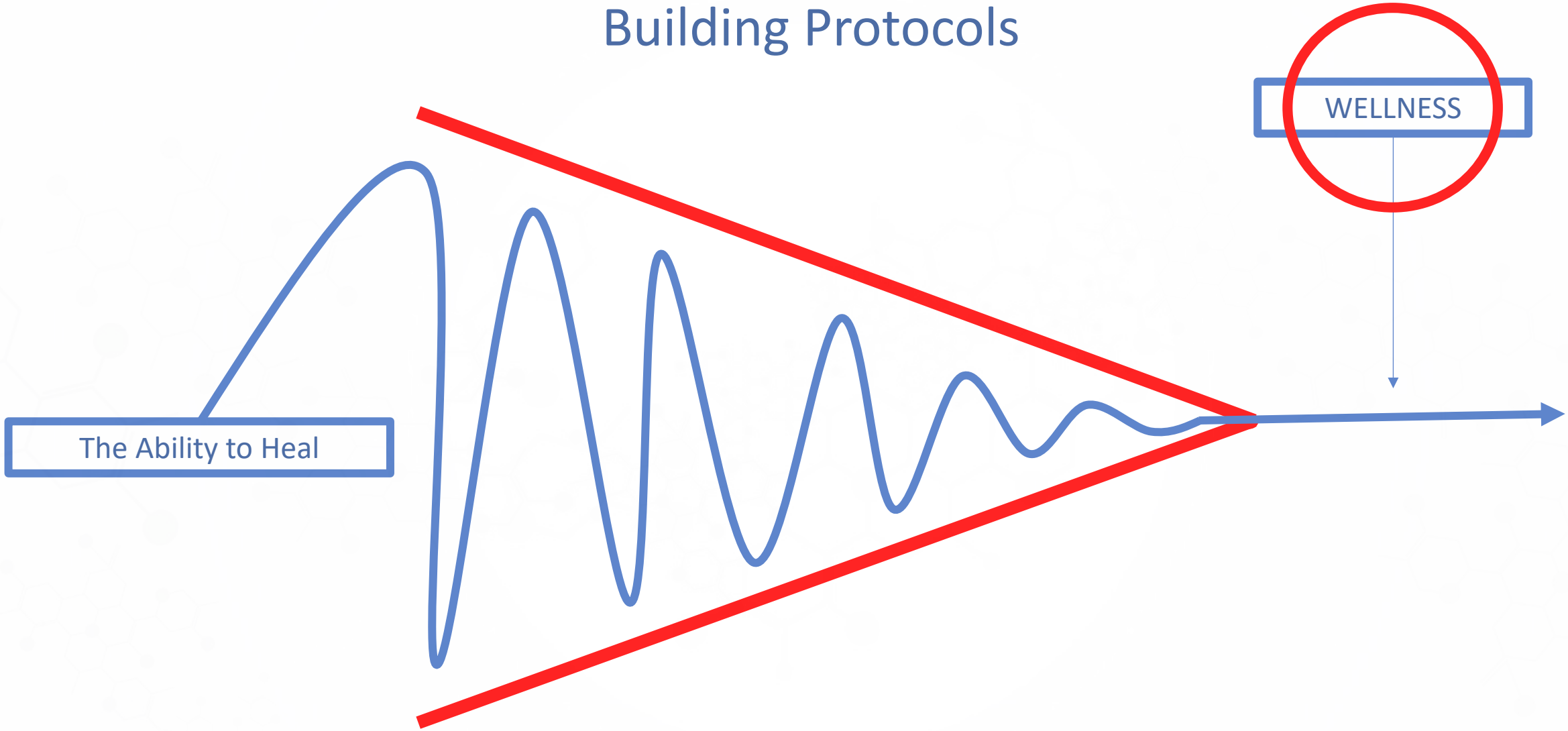
## Male PCOS Equivalent Exists: A New Syndrome?

PCOS is a very common endocrine disorder in women of reproductive age, with a prevalence of 6-15% (134). A genetic background and environmental factors are involved in its etiology. Despite PCOS diagnostic criteria mainly include hyperandrogenism, oligo-ovulation, or anovulation and polycystic ovaries (135), the role of metabolic dysfunction in the pathogenesis of this syndrome is widely accepted. Indeed, up to 75% of patients with PCOS are insulin-resistant and some are hyperinsulinemic (135). Accordingly, the presence of polycystic ovaries, which gave the name to the syndrome, is only one of the many downstream clinical manifestations of PCOS and it is not the pivotal pathogenic factor leading to the development of this syndrome (136, 137).

Since a genetic background has been observed in PCOS, this hereditary predisposition can be potentially inherited by the male sibling of the affected patients. Interestingly, the brothers and the relatives of women with PCOS have a high prevalence of hormonal and metabolic abnormalities (138–140). They also show a greater prevalence of early-onset androgenetic alopecia (AGA) (141), which has been suggested as a clinical sign of the male PCOS equivalent (142–144). The occurrence of hormonal and metabolic abnormalities in men with early-onset AGA (younger than 35 years) has been reported (145, 146) (Table 1). A meta-analytic study performed in 1009 unrelated men found increased luteotropic hormone (LH) and dehydroepiandrosterone (DHEAS), decreased sex hormone-binding globulin (SHBG), a downward trend for FSH and an upward trend for the LH/FSH ratio in patients with early-onset AGA compared with controls. This hormonal pattern somewhat resembles that found in female PCOS. The same meta-analysis showed a significant increase in insulin levels and HOMA index, total and LDL cholesterol and triglycerides in patients vs. controls, already before the age of 35 (147).


Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
PROLONGED INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Herbicides
Alcohol
Lectins
Refined Sugars
Preservatives

# Building Protocols



Protein: plant and fish-based proteins most beneficial
Vit D: optimization is key for immune balance and inflammation management
Lycopene: 15mg per day to lessen BPH
Green Tea: EGCG demonstrates benefit on relieving symptomatic BPH and LUTS
Zinc: <100mg per day helpful, >100mg per day increased risk of prostate cancer
Saw Palmetto: DHT inhibitor
Beta Sitosterol: pecans, avocado, pumpkin seeds

Alcohol: <25 oz per month to control BPH
Starch: white bread, pasta, rice – positive correlation with BPH

file:///Users/bt/Downloads/Nutrition_and_benign_prostatic_hyperplasia.9.pdf

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