

Diet/Lifestyle Strategies for Preventing Benign Prostatic Hyperplasia

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Abstract

Although benign prostatic hyperplasia (BPH) is often viewed as an inevitable concomitant of the aging process, recent research establishes that this syndrome is significantly more common in men with metabolic syndrome. Moreover, twentieth century epidemiology focusing on quasi-vegan rural China reveals that this syndrome may in fact be substantially preventable. The decline in cellular apoptosis which appears to be a key driver of BPH should be counteracted in part by diet/lifestyle measures which minimize systemic IGF-I activity. Diets moderate in protein and very low in animal products are associated with low plasma IGF-I levels, reflecting decreased hepatic production of this hormone. Leanness, exercise training, and other lifestyle measures which minimize diurnal insulin secretion, have been found to correlate with reduced BPH risk, and can be expected to reduce systemic and prostatic IGF-I/IGF-II bioactivity by increasing hepatic secretion of IGFBP-1. Apoptosis of prostate cells can also be promoted by selective agonists for estrogen receptor- β ; high dietary intakes of soy isoflavones can function as such agonists. Conversion of prostate epithelial and stromal cells to a myofibroblast phenotype by transforming growth factor- β contributes importantly to the expansion of the stromal compartment in BPH; there is reason to suspect that this transition could be opposed by the antioxidant activity of spirulina, AMPK-activating drugs or nutraceuticals, and possibly adiponectin (suggesting a further benefit of leanness). Although calcitriol analogs appear to have potential for preventing and treating BPH, there is no current evidence that dietary modulation of vitamin D status can be beneficial in this regard. Prospects for prevention of BPH may be good in individuals who adopt optimally health-protective diet, lifestyle, and nutraceutical strategies.

Benign Prostatic Hyperplasia – A Component of the Metabolic Syndrome

Benign prostatic hyperplasia (BPH) is often thought of as an inevitable concomitant of aging, as prostate volume increases progressively with age; in the U.S., prevalence of symptomatic BPH has been estimated as 50% at age 60 and 80% at age 85.¹ Nonetheless, recent studies demonstrate that, at any given age, BPH and associated lower urinary tract symptoms (LUTS) are significantly more common in men with metabolic syndrome.^{2, 3} Pioneering research by Hammersten and Hogstedt demonstrated that both prevalent BPH and annual prostate growth rate correlate positively with fasting serum insulin as well as other typical features of this syndrome, including waist circumference, blood pressure, and low HDL;^{4, 5} subsequent research has confirmed these associations, and has also demonstrated that LUTS is more common in metabolic syndrome.⁶⁻¹⁰ The link between hyperinsulinemia and BPH risk remains strong in multiple regression analyses.^{5, 11} Moreover, regular exercise and moderate alcohol consumption, independent of body weight, are associated with decreased BPH risk, and of course tends to down-regulate insulin levels by favorably impacting muscle insulin sensitivity.¹²⁻¹⁵ These findings suggest that elevated diurnal insulin may play a pathogenic role in BPH and LUTS, and may be largely responsible for the association of these conditions with metabolic syndrome. Commentators have suggested that hyperinsulinemia may both promote prostate growth, while also abetting LUTS via its stimulatory impact

on sympathetic activity.^{5, 7} The possibility that pro-inflammatory ectopic fat metabolites, or elevated CRP,¹⁶ contributes to the progression of BPH in metabolic syndrome cannot currently be ruled out. It is reasonable to suspect that diet and lifestyle choices which avoid metabolic syndrome, and act in other ways to minimize diurnal insulin secretion, may have some utility for preventing or at least postponing the onset of BPH and LUTS.

Former Rarity of BPH in Rural China

Indeed, epidemiology focusing on rural Asian societies in the last century suggests that scope for prevention of BPH may be much more substantial than previously suspected. Symptomatic BPH appears to once have been relatively rare in rural East Asians. In particular, Gu cites an autopsy study published in 1936 in which 6.6% of Chinese men over age 40 were found to have an enlarged prostate, as compared to 47% of non-Chinese men living in China autopsied by the same doctors.¹⁷ In Gu's own study, published in 1997, 413 rural and 419 urban males over age 40, living in the vicinity of Beijing, were clinically evaluated; in every age bracket, prevalence of prostate-related symptoms and prostate size was notably lower in the rural men.¹⁸ For example, in men over 70, prostate symptoms were noted in 3.2% of rural and 11.85% of urban men; estimated prostate size averaged about 50 % greater in the urban men (19.1 ml vs. 28.5 ml). Consistent with these findings, residual volume of urine after voiding was about twice as high in the urban men (16.1 ml vs. 30.0 ml). Gu also determined that, 10 years prior to the time of examination, monthly intake of animal protein had been 5-fold or more greater in the urban men than in the rural men; most of the rural men had eaten a quasi-vegan diet for most of their lives. Gu suggested that comparatively low intake of animal protein, fat, and calories may have exerted an anti-anabolic effect that protected the rural men from BPH. He also postulated a role for dietary phytoestrogens in this regard. As we shall see, in light of current knowledge, Gu's analysis emerges as exceptionally insightful. Importantly, Gu noted that prevalence of BPH in urban Chinese was now approaching Western levels – indicating that genetic factors were unlikely to account for the former rarity of BPH in China.

Curiously, Gu did not report on the relative body sizes of the rural and urban populations he examined. It can however be presumed that prevalence of obesity in the urban population at high risk for BPH was then considerably lower than it now is in the West.

IGF-I Bioactivity as a Determinant of Risk

Biopsy studies reveal that a decrease in apoptosis in both the epithelial and stromal components of the prostate – rather than an increase in proliferation – appears to play a key role in prostate hyperplasia.¹⁹⁻²¹ In addition, an epidermal-mesenchymal transition mediated by transforming growth factor-beta (TGF- β), as well as a fibroblast to myofibroblast transdifferentiation driven by this hormone, is thought to contribute to the expansion of the stromal compartment in BPH.^{21, 22}

Both the epithelial and stromal cells of the prostate express IGF-I receptors; stimulation of these receptors promotes proliferation and inhibits apoptosis in these cells.²³⁻²⁵ Although some of the IGF activity of the prostate is of autocrine origin – stromal cells can secrete IGF-II²⁴ – there is reason to suspect that systemic IGF-I activity influences prostate growth. Hence, prostate hyperplasia is a feature of acromegaly that tends to remit when GH production is controlled.^{26, 27} Conversely, underdevelopment of both the epithelial and stromal components of the prostate is observed in genetically GH-deficient mice – an abnormality that is corrected by administration of IGF-I.²⁴ Kleinberg and colleagues demonstrated that

continual infusion of IGFBP-1 (which inhibits IGF activity by binding to both IGF-I and IGF-II²⁸) inhibits prostate weight and promotes apoptosis in both epithelial and stromal prostate cells in normal male mice.²⁹

These findings accord nicely with those of a case-control study of BPH (512 total subjects) conducted in the Shanghai area.³⁰ Age-adjusted odds ratio for BPH was found to be significantly higher in the top tertile of serum IGF-I (1.89) than in the bottom tertile (1.00); the odds ratio in this tertile was even larger (2.85) after adjustment for IGFBP-1 and -3 levels. These findings clearly support a role for IGF-I in the genesis of BPH. Two previous smaller epidemiological studies focusing on European populations had attempted to correlate serum IGF-I with BPH risk.^{31,32} This relationship was confirmed in one of these studies, but not the other. The Chinese researchers suggested that the failure of the latter study to find a correlation between BPH risk and IGF-I may have reflected its small size and its failure to correct for IGF binding protein levels (which notably strengthened this association in the Chinese study).

Of related interest is a study which examined correlates of LUTS in men over 60 who participated in the cross-sectional NHANES III. Increased IGF-I was non-significantly associated with LUTS (OR = 3.20; CI 0.89-11.4), whereas the IGF-I antagonist IGFBP-3 correlated inversely with LUTS risk (OR = 0.25; CI 0.08-0.81).³³

Some investigators have observed that tallness and increased lean body mass correlate with increased risk or BPH.^{4,11} Arguably, these parameters could be correlates of increased systemic IGF-I activity, which mediates their association with BPH.

The relevance of these findings to metabolic syndrome and hyperinsulinemia is straightforward. Hyperinsulinemia can increase the effective bioactivity of circulating IGF-I by suppressing hepatic secretion of IGFBP-1, a functional antagonist of this hormone.^{34,35} Moreover, IGFBP-1 of hepatic origin also has the potential to inhibit the activity of IGF-I or IGF-II produced within the prostate.³⁶ The utility of IGFBP-1 infusion for decreasing prostate weight in mice has been noted.²⁹ It is therefore reasonable to suspect that protection from BPH afforded by leanness and regular exercise reflects, at least in part, lower IGF-I/IGF-II activity within the prostate. However, low diurnal insulin may also reduce risk for LUTS by moderating sympathetic activity.⁷

It is now clear that vegans consuming diets of moderate protein content tend to have relatively low serum levels of IGF-I relative to omnivores.³⁷⁻³⁹ This likely reflects an inhibitory effect of borderline essential amino acid status on hepatic IGF-I secretion, as is well established in rodents and cultured hepatocytes.⁴⁰ It is reasonable to speculate that the virtual absence of “high-quality” animal protein in the diets of Chinese farmers during past decades – in conjunction with relative leanness and frequent physical activity – may have been a key mediator of the low risk for BPH in rural Chinese noted by Gu and previous observers, owing to relatively low systemic IGF-I activity.

In addition to its down-regulatory impact on plasma IGF-I, a whole-food plant-based diet, consumed *ad libitum*, tends to promote leanness and good insulin sensitivity^{41,42} – possibly in part because such diets have a low saturate-unsaturate ratio.⁴³

Estrogen Receptor- β Agonists Boost Apoptosis in the Prostate

Gu may also have been right in suggesting a role for phytoestrogens in prevention of BPH. Risbridger and colleagues have shown that agonists specific for the beta isoform of the estrogen receptor (ER- β) promote apoptosis of stromal as well as basal and luminal epithelial compartments of mouse prostate; a similar effect is seen when human BPH tissue is xenografted into mice.^{44, 45} This apoptosis is mediated by induced expression of TNF- α and activation of caspase-8. The authors suggest that ER- β -specific agonists may have potential in the prevention and treatment of BPH. There is evidence that, when ingested in physiological amounts provided by normal diets, soy isoflavones achieve selective activation of ER- β , with minimal impact on ER- α activity (and hence no feminizing symptoms). Hence, it is conceivable that frequent ingestion of soy products may have contributed to lower risk for BPH in East Asians consuming traditional diets. Consistent with this possibility is a report that dietary intake of isoflavones correlates inversely with risk for lower urinary tract symptoms (LUTS) in a prospective cohort of 2,000 men in Hong Kong.⁴⁶ The first controlled clinical trial to evaluate soy isoflavone supplementation in men with symptomatic BPH (40 mg daily – possibly a sub-optimal dose) has concluded that the isoflavones were slightly more effective than placebo for alleviating symptoms.⁴⁷

Countering Myofibroblast Generation

As noted, TGF- β -driven myofibroblast generation may play a key role in the etiology of BPH. Exposure of human primary prostatic fibroblasts to TGF- β leads to induction of NOX4 and increased oxidant stress, which in turn activates c-Jun N-terminal kinase (JNK).²² This sequence plays a key role in the phenotypic shift toward myofibroblast behavior, as this shift is blocked if NOX4 is knocked down or inhibited, or if JNK is inhibited. There is recent evidence that intracellular bilirubin derived from heme oxygenase activity functions as a potent feedback inhibitor of NADPH oxidase activity – including that of NOX4⁴⁸ – and that the phycochemical phycocyanobilin (PhyCB) richly supplied by spirulina can mimic this effect.⁴⁹⁻⁵² Hence, it is credible to suggest that a sufficient intake of spirulina or of PhyCB might help to prevent BPH by suppressing myofibroblast induction.

Moreover, AMPK activation has been reported to inhibit myofibroblast transdifferentiation of TGF- β -treated fibroblasts.^{53, 54} Although AMPK does not influence the phosphorylation or nuclear translocation of Smad3, it appears to block association of Smad3 with its coactivator p300, and thereby suppress Smad3-mediated transcription. Furthermore, AMPK could be expected to exert anti-hyperplastic activity via inhibition of mTORC1.^{55, 56} And hepatic activation of AMPK might be expected to favor prostate health by down-regulating diurnal insulin secretion.⁵⁷ AMPK-activating agents such as the drug metformin and the nutraceutical herbal compound berberine are now widely employed in the management of diabetes, and there is good reason to suspect that these agents may be more broadly useful for overall health promotion; indeed, some gerontologists argue that these agents have “anti-aging” potential, and that their use by healthy adults – and by non-diabetics with metabolic syndrome - should be further evaluated and possibly encouraged.⁵⁷⁻⁶¹ Hence, it would be of interest to determine whether metformin or berberine may have some utility for prevention of BPH. There do not currently appear to be any published studies that have evaluated risk for BPH in metformin-treated diabetics.

Adiponectin can activate AMPK in many tissues, and tends to be higher in leaner men who, as noted, are at somewhat lower risk for BPH. In rodent models of hepatic fibrosis, adiponectin exerts a protective effect by suppressing the impact of TGF-beta on stellate cells,^{54, 62, 63} whether adiponectin is active in

prostate stromal cells does not seem to have been assessed. A recent analysis of men enrolled in the placebo arm of the Prostate Cancer Prevention Trial concluded that a higher baseline adiponectin predicted a lower risk for new BPH in non-sedentary men during 7 years of follow-up; the investigators concluded that adiponectin might account for some but not all of the protective impact of leanness.⁶⁴ Research examining the impact of adiponectin on prostate-derived cells is required to follow this lead further.

Vitamin D Activity vs, BPH

A less-calcemic analog of calcitriol, elocalcitol, has been shown to inhibit intra-prostatic growth factor activity in pre-clinical studies, and is now being evaluated clinically in BPH.^{65, 66} Whether vitamin D status might influence risk for BPH has received little study. One Korean study failed to find a correlation between serum 25-hydroxyvitamin D and prostate size in patients with BPH; however, this study also failed to note a correlation with BMI, a known determinant of BPH risk.⁶⁷ Serum calcitriol levels are relatively high in individuals whose diets are relatively low in calcium and bioavailable phosphate^{68, 69} – a characteristic of many plant-based diets. Whether circulating calcitriol levels might be high enough to influence BPH risk has not been examined in epidemiological studies.

Summary – Potential of Diet/Lifestyle Strategies for BPH Prevention

In light of the twentieth century epidemiology of BPH in rural China, and plentiful research linking BPH to metabolic syndrome, it can be concluded that BPH is not an inevitable concomitant of aging, but rather that it is substantially preventable via appropriate lifestyle measures. The considerations cited above suggest that a plant-based diet of moderate protein content, via down-regulation of serum IGF-I, may notably reduce BPH risk. Measures which minimize diurnal insulin secretion – such as leanness, exercise training, a low dietary saturate/unsaturate ratio,⁴³ and low-glycemic-index food choices – may also reduce this risk by decreasing the effective activity of IGFs. Frequent consumption of soy isoflavones may promote apoptosis in prostate tissue by selective activation of ER- β . Spirulina (via PhyCB) and AMPK activators may have potential for suppressing the myofibroblast transdifferentiation that plays a pathogenic role in BPH. Although the calcitriol analog elocalcitol has been shown to slow prostate growth, it is not yet clear whether systemic vitamin D (serum levels of calcidiol or calcitriol) can have a meaningful influence in this regard.

With respect to the low risk for BPH once enjoyed by rural Chinese, the above analysis suggests that a diet of modest protein content very low in animal products, leanness, regular physical activity, and, in some instances, a high intake of soy isoflavones, likely contributed to this protection.

Although these suggestions are speculative at this time, it is reassuring to note that the diet/lifestyle/nutraceutical measures proposed are likely to be health protective in many other ways, and hence are recommendable whether or not they prove to be beneficial for BPH prevention. In particular, low IGF-I bioactivity, soy isoflavones, AMPK activators, leanness, and physical activity may reduce risk for prostate cancer or aggressive prostate cancer.⁷⁰⁻⁷⁵ This essay has not discussed drugs or certain herbal extracts (such as saw palmetto or pygeum Africanum) often employed in the management of BPH because its intent was to focus on measures which are likely to have broad, rather than specialized, utility for health promotion.

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