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Review

Benign prostate hyperplasia and nutrition

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SUMMARY

Background: and aims: Benign Prostatic hyperplasia (BPH) is an important public health problem. Roughly half of all men will suffer from BPH related symptoms later in life. The prostate gland, a hormone dependent part of the male reproductive system, is susceptible to internal and external disruptions of regulatory systems. We attempt in this paper to collect available evidence on influence of lifestyle modifications, and naturally occurring substances, plants, micronutrients and supplements on BPH symptoms.

Methods: Systematic review was performed within the MEDLINE database and Cochrane Library Central Search using a combination of Medical Subject Headings (MeSH) and keywords.

Results: Moderate exercise and the type and amount of protein intake have a considerable influence on BPH symptoms. The intake of zinc and vitamin D also positively influence BPH symptoms, and so do certain supplements, such as saw palmetto, cemilton and pygeum extracts.

Conclusions: Lifestyle changes, diet modification and certain nutritional supplements can favorably influence BPH symptoms.

1. Introduction

Benign prostatic hyperplasia (BPH) is an important and ubiquitous health problem, affecting almost half of all men in the later decades of their lives. The prostate being an adjunct organ to the reproductive system, it is susceptive to internal and external environmental influences on a hormonal, biochemical, micronutrient and genetic level.

In a time of increasing industrialization and industrial mass food production, humans ingest yet unknown levels of chemicals, hormones and micronutrients, that may be harmful or deregulatory for our inner environment and biochemical balance.

On the other hand, we may use the same micro-mechanisms to influence pathophysiological processes by natural means such as BPH. Thus, we may avoid synthetic drugs with their inherent side effects or delay their use, and even slow or reverse the course of the disease.

BPH is characterized by the appearance of hyperplastic nodules found primarily in the periurethral region and transition zone of the prostate where it enlarges and starts impinging on the urethra. This results in a constellation of symptoms called lower urinary tract symptoms (LUTS). These include irritative voiding symptoms such as frequency, urgency and nocturia, and obstructive symptoms such as weak urinary stream, incomplete bladder emptying, straining to void, and an intermittent stream.

This condition predominantly affects older men. About 75% of men >50 yr of age suffer from BPH related symptoms. Additionally, 20–30% of men reaching 80 yr of age require surgical intervention for the management of BPH [1,2].

BPH is a health condition with a considerable economic burden. This is related in part to direct medical costs for diagnosis and treatment, and in part indirect costs associated with the loss of work time, and intangible costs associated with a reduced quality of life (QOL). Despite its high impact on public health, the etiology and pathophysiology of this disease remains somewhat unclear, as do interventions to modify the natural history of this condition.

To date, there are no preventive or curative treatment guidelines for benign prostatic hyperplasia. Dietary and nutritional factors may influence BPH etiology and symptoms through a variety of mechanisms, but the literature on this topic is sparse [3]. Early

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interventions with lifestyle changes, dietary modifications or addition of dietary supplements may restrict the progression of this condition, avoid or delay the need for medications with considerable side effects, or surgery with related morbidity.

In this manuscript, we discuss factors that may influence the etiology and pathophysiology of the disease, and the role of lifestyle and nutrition in the progression of benign prostatic hyperplasia. We also mention the different dietary supplements that have been used for the condition and their efficacy.

2. Evidence acquisition

A systematic, structured, and comprehensive literature review was performed. Separate searches were done within the MEDLINE database and The Cochrane Library Central Search using a combination of MeSH and keywords.

The initial search terms were “benign prostatic hyperplasia” and “physiopathology”, “BPH” and “role of lifestyle, BPH and nutrition”, respectively. Based on the results of these initial searches, additional separate searches were performed using the terms “benign prostatic hyperplasia” in combination with “metabolic syndrome”, “aging”, “inflammation”, and “hormonal alterations”. Only English-language publications were considered in the final assessment.

The first search screened 100 studies, that were reduced to 24 after evaluation by title and abstract; 14 studies were retrieved by references of the selected studies; a total of 38 studies were assessed and 25 were included in the review (Table 1).

Information extracted from each study was charted including: first author's last name; year of publication; number of subjects; food or nutrients or dietary pattern studied.

Literature was evaluated using the Newcastle-Ottawa-Scale and evaluation forms (supporting documents 1–3).

3. Prevalence

Benign prostatic hyperplasia (BPH) is the fourth most common diagnosis in older men [4]. Autopsy data indicate that anatomic or microscopic evidence of BPH is present in 40% and 90% of men aged 50–60 and 80–90 y, respectively [5]. It has been postulated that the incidence of BPH increases by 10% per decade of lifetime. Benign prostatic hyperplasia is more common in North America and Europe than in Asia, particularly in China. International variation is frequently considered a powerful argument for emphasizing the importance of environmental factors, including dietary habits. It has been suggested that the lower incidence of BPH in China could be related to higher garlic consumption in China [6].

To understand the multifactorial changes leading to BPH as a pathophysiological alteration resulting in a symptom complex within the inner and outer environment of a male human being, it may help to first outline what is known about its etiology and pathophysiology to date.

4. Etiology

The etiology of BPH is unclear, but it appears to represent a multifactorial process involving both, mechanical and dynamic components [7]. Prostatic enlargement represents the static or mechanical component, and lower urinary tract symptoms due to a heightened tone of the prostatic smooth muscle account for the dynamic component of BPH. The dynamic component is controlled by the sympathetic nervous system.

The only two well-established factors associated with BPH are the presence of androgens and age [8]. In the population-based Olmsted County study, moderate to severe urinary symptoms were recorded in 13% of men 40–49 yr of age versus 28% in subjects >70 yr [9]. The median rate of prostatic volume change is 0.6 ml per year of age, corresponding to a median growth rate of 2.5% per year [10]. In ageing males, a significant tissue-remodeling process takes place within the prostate with an increase in gland volume [11].

Androgens do not cause BPH, but the presence of androgens is a necessary factor for BPH to develop [12]. Patients castrated before puberty do not get BPH. Similarly, BPH is absent in men with genetic diseases that impair androgen action or production. Other proposed risk factors include metabolic syndrome, diabetes mellitus, obesity, race, and cardiovascular disease [13] (Fig. 1). Especially, abdominal obesity and genetic factors have been postulated as important risk factors for the development of BPH which appears to run in families. If one or more first-degree relatives are affected, an individual is at greater risk of developing the disorder. Waist size, body mass index, and increase in body weight also appear to increase the volume of the prostate gland [14].

5. Pathophysiology

In ageing men, serum testosterone levels decrease and estrogen, prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels rise. Estrogen increases the number of androgen (DHT) receptors in the prostate and inhibits androgen metabolism by interfering with hydroxylation. This leads to a significant tissue-remodeling process within the prostate, especially in the transition zone (TZ). Interference in the delicate balance of interacting growth factor signaling pathways occurs, and stromal–epithelial interactions generate an increase in prostate volume. Additionally,

Table 1
Evidence acquisition from the literature searches.

Article screened	100
Selected by title and abstract	24
Retrieved from references	14
Full text assessed for eligibility	38
Studies included	25

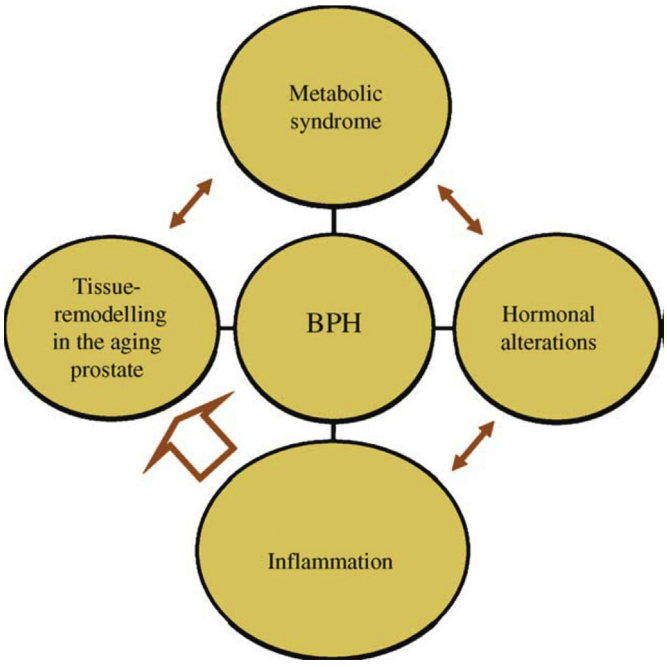

Fig. 1. Relationship between age, metabolic syndrome, inflammation, hormonal alterations, and benign prostatic hyperplasia (BPH) [11].

there is a substantial net decrease of apoptosis in both, the glandular and basal epithelial cell compartments resulting in a growth imbalance in favor of cell proliferation [14]. BPH is also associated with chronic inflammation, which support the fibromuscular growth. There is disseminated infiltration by activated T and B lymphocytes and numerous colonies of macrophages. Upregulation of pro-inflammatory cytokines interleukin (IL)-15 in stromal cells [15], IL-17 in infiltrating T cells [16], interferon-g in basal and stromal cells [17], and IL-8 in epithelial cells drive local growth factor production and angiogenesis in the tissues as a "wound healing" response. Local hypoxia because of increased oxygen demands of proliferating cells also may play a role in the pathophysiology of BPH. This promotes neovascularization and fibroblast-to-myofibroblast transformation, triggering prostatic growth [18]. Finally, prostaglandins, leukotrienes, and insulin resistance have also been proposed to play a role in the inflammatory process of the prostate. Components of the metabolic syndrome do cause prostatic enlargement. In a Swedish study of 250 patients with BPH, annual BPH growth rate correlated positively with diastolic blood pressure ($p = 0.01$), body mass index (BMI) ($p < 0.001$), and fasting plasma insulin level ($p = 0.008$), and negatively correlated with HDL-C level ($p = 0.001$) [19].

A greater waist-to-hip ratio and a higher serum insulin increase the risk for BPH [20]. Elevated insulin levels increase sympathetic nerve activity and bind to insulin-like growth factor (IGF) receptors that stimulate prostate cell growth. Additionally, hyperinsulinemia suppresses liver production of sex hormone binding globulin (SHBG) to increase free testosterone. Excessive amounts of visceral fat also increase the circulation of estradiol and further stimulate prostate cell growth by increasing DHT levels (Fig. 2). Obesity, metabolic syndrome, and insulin resistance all increase systemic inflammation, which in turn is correlated with the incidence of BPH [21].

With the progressive increase in prostate volume, urinary outflow obstruction develops. The detrusor muscle of the bladder tries to compensate by increasing pressure to expel urine, a process that leads to instability of the muscle and worsening symptoms. This leads to symptoms of BPH and obstruction of the lower urinary tract that, in turn, cause detrusor muscle dysfunction. Stimulation of the alpha-adrenergic system leads to contraction of the smooth muscle fiber and further restricts flow in an enlarged prostate gland.

6. Role of lifestyle in BPH

Understanding the direct influence of lifestyle changes on the prostate gland is limited by the difficulties in obtaining prostate tissue from healthy men before and after lifestyle intervention. Albeit, some of the factors that have been implicated in playing a role—inflammation, elevated plasma levels of estrogens, insulin, and IGF-I—are all amenable to reduction through proper lifestyle change. Epidemiological studies report an increased risk for BPH with a high caloric, protein, and polyunsaturated fatty acid intake. Inverse associations have been reported for consumption of fruits and vegetables [3,22,23]. Physical activity has also been reported to reduce the risk for BPH and/or LUTS. In the pooled analyses, light physical activity was associated with a nonsignificant trend towards a decreased risk for BPH and LUTS. Moderate or vigorous physical activity was associated with an odds ratio [OR] of 0.74 for BPH and LUTS [2]. Regular exercise (5 days a week), combined with a low-fat diet of whole grains, fruits, and vegetables, has been shown to lower insulin and IGF1 levels, and elevate IGFBP-1 levels with a consequent reduction in growth of prostate cells and an increase in apoptosis. In these subjects, there was also a decline in inflammatory cytokines produced via the nuclear factor-κB (NF-κB) pathway that stimulates growth and blocks apoptosis. Further studies have shown moderate exercise coupled with low fat diet resulted in downregulation of RAS oncogenes (RAN, RAB14, and RAB8A) and SHOC2, which encodes a protein essential for MAPK activation by growth factors, thereby reducing the risk of BPH [24].

7. Influence of diet in BPH

7.1. Total energy intake and type of diet

Intakes of total energy and specific macronutrients may affect several aspects of the underlying etiology of BPH and resulting lower urinary tract symptoms. A community based study spanning 8 years that surveyed the details of diet of a large cohort of

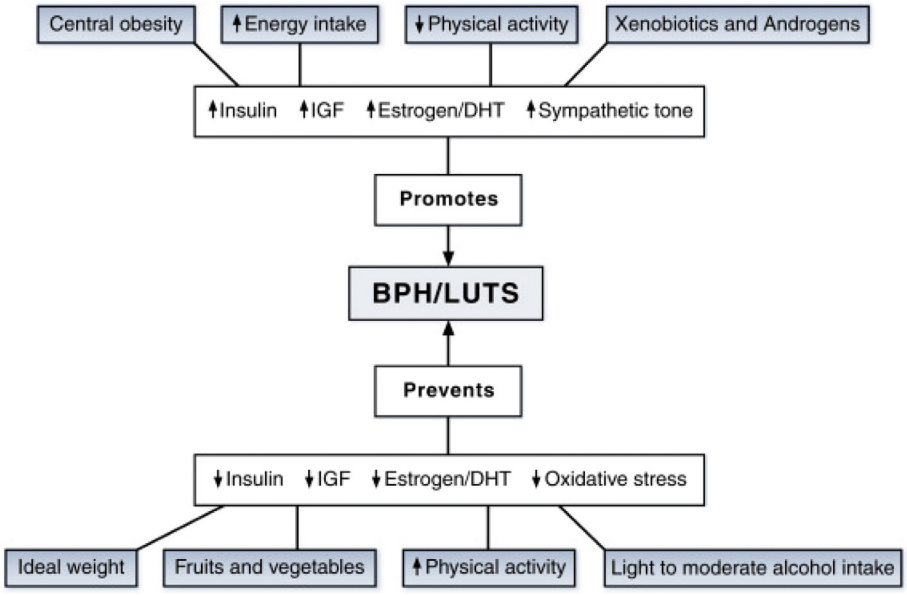

Fig. 2. Influences affecting the promotion and prevention of benign prostatic hypertrophy (BPH) and lower urinary tract symptoms (LUTS). DHT = dihydrotestosterone; IGF = insulin-like growth factor [22].

Health Professionals with BPH reported a modest direct association between BPH and intakes of total energy, protein and specific long chain polyunsaturated fatty acids [3]. Though energy adjusted total protein intake was positively associated with BPH and BPH surgery in their multivariate analysis, no relation of total fat or carbohydrate intake with BPH incidence was observed. A larger association of BPH has been reported with animal protein than vegetable protein [3,4]. It may be advisable to include high-quality plant based protein and cold water fish-based protein in the diet than consuming large amounts of animal protein. High consumption of unsaturated fatty acids may contribute to lipid peroxidation of the cell membrane and of the components and fluidity of cell membranes, which may affect 5α-reductase activity [25]. Conflicting outcomes have been reported regarding the association of fatty acid intake and BPH. The Heath Professionals Follow-up Study and a Greek case control study suggested a direct association between polyunsaturated fatty acids and BPH [3,26], whereas a large Italian study reported an inverse correlation between fatty acid intake and BPH risk [22]. In this study, linolenic and linoleic acids showed a protective role against BPH. The fatty acid composition of the diet influences the level of endogenous cholesterol which is involved in the synthesis of steroid hormones, and associated with BPH risk. High energy intake may increase abdominal obesity and sympathetic nervous system activity, both of which may increase the risk of BPH [27]. The activation of the sympathetic nervous system and the consequent activation of prostatic smooth muscles may lead to worsening of lower urinary tract symptoms [28]. The Health Professionals Follow-up Study showed increased association of BPH and LUTS with increased total energy intake but no correlation was observed between total energy intake and BPH related surgery [3]. Another community based study showed total energy and sodium intake were positively associated with LUTS, whereas greater protein intake was inversely associated with LUTS [29]. These observations suggest the effect of energy intake on BPH is mediated through the dynamic rather than the static component of BPH. Dietary starch intake has been shown to have a positive association with BPH [22]. Starch may be responsible for a glycemic overload that is compensated for by an increase in serum insulin and insulin-like growth factor, which are thought to stimulate BPH. The main sources of starch in this study population were bread, pasta and rice. No association has been found between sugars obtained from fruit, which have a lower glycemic index than bread [30].

7.2. Soy

Soy is an inhibitor of 5-alpha-reductase and a low-potency estrogen. Consumption of non-fermented soy products (tofu, soy milk, edamame) results in a decreased incidence of prostate cancer [31]. Soy may block the receptor sites that the stronger estrogens use to increase the accumulation of DHT. Thereby it influences the natural history of BPH.

7.3. Cholesterol

Cholesterol has been associated with both, BPH and prostate cancer. Metabolites of cholesterol (epoxycholesterols) have been identified in the hyperplastic and cancerous prostate gland. Hypocholesterolemic drugs (3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors, or “statins”) lower the risk of both, BPH and prostate cancer [32,33]. Foods high in cholesterol and saturated fat are rich in arachidonic acid as well, which is the main precursor of inflammation. Reducing consumption of these foods can benefit BPH patients by reducing inflammatory triggers. In patients with metabolic syndrome, following a low-glycemic load diet and exercise improves both, dyslipidemia and BPH symptoms.

7.4. Omega-3 fatty acids

Foods rich in omega 3 fatty acids include cold-water fish (salmon, mackerel, sardines), vegetables, and ground flaxseed or flaxseed oil. A diet rich in omega-3 fatty acids helps to reduce the influence of prostaglandins and leukotrienes on the inflammatory component of BPH [21]. Whole Flaxseed seeds (Flaxeed oil, also available as 500 mg capsules) has the added benefit of lignan fibers, which help to bind estrogen in the gut and thus promote estrogen removal. Thereby they influence the progression of BPH. To the contrary, a high intake of eicosapentanoic acid and docosahexanoic acid was associated with higher prevalence of BPH, lower urinary tract symptoms and BPH related surger. Their high degree of unsaturation promotes lipid peroxidation which in turn leads to an increase in 5α reductase and prostatic dihydrotestosterone, increasing epithelial and stromal growth. Increased levels of omega 3 fatty acids were associated with the mechanical, or static, component rather than with the dynamic component of BPH [3].

7.5. Onion and garlic

A multitude of benefits have been linked to Allium vegetables, namely favorable effects on cardiovascular disease, anti-proliferative action on human cancers, and prevention of diseases associated with aging [6]. Garlic and its constituents inhibit key enzymes involved in cholesterol and fatty acid synthesis. Endogenous cholesterol is involved in the synthesis of steroid hormones and is associated with a BPH risk. In addition, onion and garlic contain vitamins and enzymes, and are rich in phytochemicals with antioxidant properties. Significant improvement in disease parameters has been reported in BPH patients who regularly consumed aqueous garlic extracts [34]. A low incidence of BPH in Asian countries, predominantly China has been attributed to increased consumption of garlic in Chinese nationals [35].

7.6. Alcohol and smoking

A high alcohol intake may be associated with BPH. The association was most significant for beer, wine, and sake, and less so for distilled spirits. Most recent studies however confirm a protective effect of alcohol with regard to BPH, but not with LUTS [4].

The influence of smoking on BPH is rather controversially discussed. Some postulate an inverse, protective effect of smoking on BPH, and others refute this [13,36].

7.7. Zinc

Few studies have shown the protective effect of Zinc against BPH [4,21]. A decrease in zinc levels in plasma and prostate tissue in men with BPH (and prostate cancer) has been reported [4]. Zinc supplementation resulted in a reduction of prostate size as well as symptoms of BPH. This may be attributed to blockade of 5-alpha-reductase and/or inhibition of prolactin, resulting in the decreased uptake of testosterone by the prostate and consequent conversion to dihydrotestosterone [4,37]. It also inhibits the binding of androgens to their receptors in the prostate [37]. Pumpkin seeds are a rich source of zinc, and this may explain their potential therapeutic benefit for BPH. Despite the protective role of zinc against BPH, excessive consumption of zinc (>100 mg/day) should be avoided as it may increase the risk of advanced prostate cancer [38].

7.8. Coffee

Coffee can decrease zinc absorption by 50%. Further, caffeine stimulates the adrenergic nervous system (smooth muscles of the prostate) and may worsen BPH symptoms [21]. Patients with BPH may benefit from a reduced caffeine intake.

7.9. Amino acids

The combination of glycine, alanine, and glutamic acid (in the form of two 6-grain capsules administered three times daily for 2 weeks, and one capsule three times daily thereafter) has been shown in several studies to relieve many BPH symptoms. In one controlled study, nocturia was relieved or reduced in 95%, urgency reduced in 81%, frequency reduced in 73%, and delayed micturition alleviated in 70%, respectively [4]. The probable mechanism of action is the amino acids acting as inhibitory neurotransmitters thus reducing the feeling of a full bladder. Therefore, amino acid therapy addresses only symptoms.

7.10. Cranberry

The phenols found in cranberry and other dark colored grapes and berries may help with the symptoms of LUTS. In a study of 21 men, those with cranberry supplementation (500 mg thrice daily for 6 months) showed a greater improvement in their IPSS, quality of life, and urinary flow measurements than a control group [21].

7.11. Vitamin D

An increased intake of vitamin D from diet and supplements has shown a correlation with a decrease in BPH prevalence. Vitamin D attaches to its receptors in the prostate and bladder and inhibits prostate growth, lowers excessive contractility, and reduces inflammation [39]. It also has an inhibitory effect on the RhoA/ROCK pathway, along with cyclooxygenase-2 expression and prostaglandin E2 production in BPH stromal cells. Vitamin D analogues of up to 6000 IU/day have shown to decrease the prostate volume in BPH patients [40].

8. Other dietary supplements (Table 2)

According to the US Dietary Supplement Health and Education Act, the definition of a dietary supplement is a product for oral administration that is intended to supplement the diet and that contains dietary ingredients such as vitamins, minerals, botanicals, and amino acids [41].

8.1. Cadmium

Cadmium is an antagonist of zinc and increases 5-alpha-reductase activity. However, its concentration in the prostate and its effects are unclear. Several studies have produced conflicting results [4].

8.2. Lycopene

Lycopene is a component of tomatoes. A randomized double-blind placebo-controlled trial reported that Lycopene may inhibit BPH progression and ameliorate BPH related symptoms [42]. Lycopene supplements are safe and well tolerated [4].

8.3. Beta-sitosterol

Beta-sitosterol is a major component of a group of plant sterols called phytosterols. They have a similar composition to cholesterol. Unlike cholesterol, beta-sitosterol cannot be converted to testosterone. It also inhibits aromatase and 5-alpha-reductase. A double-blind, placebo-controlled study using a 20-mg dose of Beta-sitosterol reported increased urinary flow and decreased residual volume in the bladder in the treatment arm [43].

8.4. Saw palmetto (Serenoa repens)

Saw palmetto has three positive effects on the prostate gland: anti-androgenic, anti-proliferative, and anti-inflammatory [21]. It is a weak inhibitor of 5-alpha-reductase. It also reduces the number of estrogen and androgen (DHT) receptors. Saw palmetto inhibits fibroblast growth factor and epidermal growth factor, and stimulates apoptosis thus further slowing prostate cell proliferation. Its principle ingredient, beta-sitosterol, is also found in soy products (see above), as well as in other herbs used to treat diseases of the prostate including pygeum bark, stinging nettle root, and pumpkin seed extract. Saw palmetto has not shown any benefit in reducing the size of prostate. However, it has been found to improve symptom scores, nocturia, residual urine volume, and urinary flow in patients with BPH.

8.5. Rye grass pollen

Rye grass pollen is also known as *grass pollen* and *grass pollen extract*. Clinical studies used a form called Cernilton (flower pollen), a brand manufactured by Cernitin. This has been bought by the company Graminex and is now marketed under the name of PollenAid. This extract has been in use for more than 35 years. In double blind studies, a response rate of over 70% has been reported [4,21]. It works by inhibiting prostatic cell growth. It also reduces inflammation of the prostate by inhibiting prostaglandins and leukotrienes.

8.6. Pygeum africanum (synonym: Prunus africana)

It is obtained from the bark of the African plum tree. It benefits through its constituent fatty acids that reduce inflammation

Table 2
Recommended dosage and side effects of commonly used nutritional supplements used for BPH.

Supplement	Dosage	Side Effects
Lycopene	15 mg OD	Gastrointestinal side effects
Beta-sitosterol	60 mg BID (reduce to 30 mg BID once symptoms improve)	Gastrointestinal side effects
Saw palmetto	160 mg BID	Headache, nausea, diarrhea, and dizziness
Rye grass pollen	126 mg TID	
Graminex Pollen Aid (formulation of RGP)	500 mg TID	Abdominal distention, heartburn, and nausea
ProstaFlo (formulation of RGP)	320 mg; 3–5 capsules/day	
Pygeum africanum	100–200 mg OD	Nausea and abdominal pain

Legend: RGP = rye grass pollen; OD = once daily; BID = twice daily; TID = three times daily.

through the inhibition of prostaglandins, as well as prostatic cholesterol levels that are precursors to testosterone production. Pygeum also increases prostatic and seminal fluid secretions [4,21]. The TRIUMPH study that included treatment outcomes of BPH from six European countries, showed a 43% improvement in IPSS scores and an improvement in quality of life with Pygeum compared to a no treatment arm [44].

8.7. *Urtica dioica (stinging nettle)*

Extracts of the root of *U. dioica* are effective in the treatment of BPH. Three double-blind studies have shown it to be more effective than placebo [4]. The most recent study, conducted in Iran, was a 6-month double-blind placebo-controlled randomized partial cross-over comparative trial of *Urtica* with placebo in 620 patients (two capsules of 300 mg each, 2 times a day) [45]. Both groups continued the medication up to 18 months and only those who continued the therapy, had favorable results. No side effects were identified in either group.

9. Conclusion

Therapeutic goals in BPH include normalization of prostate nutrient levels, restoration of steroid hormones to normal levels, inhibition of overproduction of DHT, reduction of inflammatory processes, and limitation of promoters of hyperplastic process. Altering the progression of BPH by lifestyle modification, dietary changes or supplementation with nutritional supplements is long known but not widely adapted. Performing moderate exercise 4–6 times a week, following a diet rich in vegetable protein and low in animal protein, fortification of diet with zinc and Vitamin D rich foods and intake of supplements like Saw palmetto, Cemilton and Pygeum extracts may help in controlling prostate growth and related LUTS.

Authors contributions

KD did the literature research and wrote various drafts of the manuscript.

NB initiated the project, supervised the work, edited the final paper, added introduction and synopsis, and submitted the paper.

Competing interests

None of the authors declare competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.07.015.

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