The Effect of Phytosterols on Quality of Life in the Treatment of Benign Prostatic Hyperplasia

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In the United States, phytosterols are available as over-the-counter dietary supplements and are promoted as a safe and natural way to maintain a healthy prostate. In men with benign prostatic hyperplasia (BPH), evidence suggests that the agents improve urologic symptoms and flow measures to a greater extent than placebo and to a similar extent as finasteride. The primary goal for treating men with BPH is to reduce lower urinary tract symptoms and increase quality of life (QOL). Therefore, QOL has become an increasingly important end point in clinical trials. We reviewed all seven studies that determined the effect of phytosterols on QOL in patients with BPH. All trials assessed QOL with international prostate symptom score questions. Six studies found phytosterols to have beneficial effects on QOL; however, poor study design limits what can be learned from these evaluations. Most studies included a limited number of patients, and many were not placebo controlled. Since few of them evaluated the effect of phytosterols beyond 6 months, little evidence exists of the agents' long-term efficacy in reducing symptomatology or increasing QOL. Finally, phytosterols have not been adequately compared with α-blocking agents, one of the most widely administered and effective pharmacologic treatments of BPH. Larger studies comparing phytosterols with other treatments of BPH such as α-blockers should be conducted. In addition, a consensus should be reached as to which questionnaires are best to evaluate potential changes in QOL after treatment of BPH.
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OUTLINE

Phytosterols are readily available over the counter as dietary supplements in the United States, and are promoted as a safe and natural way for men to maintain a healthy prostate.[1] In 1999 consumers in this country spent over $140 million on saw palmetto (*Serenoa repens*) alone.[2] *Serenoa repens* is a dwarf palm tree that grows in the southwest United States. Extracts of the plant contain a mixture of phytosterols such as β-sitosterol, campesterol, and stigmasterol, as well as flavonoids and other compounds.[3] Phytosterols used to treat benign prostatic hyperplasia (BPH) are also extracted from *Hypoxis rooperi* (South African star grass). This extract contains β-sitosterol, with lesser amounts of other sterols, and is marketed in Europe under brand names Harzol and Azuprostat.[3] Although both plant-derived extracts contain many phytosterols, β-sitosterol often is considered the major active component.[3] The mechanism of

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action of phytosterols in BPH, although not well described, reportedly includes alterations in cholesterol metabolism; antiestrogenic, antiandrogenic, and antiinflammatory effects; and decreases in sex hormone–binding globulin.[1]

Phytosterols improved lower urinary tract symptoms (LUTS) and urinary flow measures in numerous clinical trials.[1, 4] According to a systematic review of 18 randomized, controlled studies of *S. repens* (alone or in combination with other phytotherapeutic agents) of 4–48 weeks' duration, compared with placebo, men treated with *S. repens* had decreases in LUTS scores and nocturia and greater improvement in peak urine flow.[1] Compared with finasteride, men treated with *S. repens* had similar improvements in LUTS scores and peak urine flow rates.[1]

β-Sitosterols also are efficacious in the treatment of BPH, improving urinary symptoms and flow measures in four placebo-controlled clinical trials.[4] To date, the efficacy of phytosterols has not been compared with that of α-blocking agents in the treatment of BPH.[1, 4]

The primary goals of treating BPH are to reduce LUTS and improve quality of life (QOL).[5] Quality of life includes physical, psychologic, and social domains and is a subjective perception of how a disease or treatment affects health status.[6] Despite frequent reports of use of herbal products to promote general health and well-being and to increase QOL, studies mainly focused on clinical outcomes, with QOL evaluated only occasionally as a secondary end point.[7] The American College of Clinical Pharmacy published a white paper that called for additional research on herbal products, listing QOL evaluations as an area in which further investigation is necessary.[8]

Quality of life was evaluated as a secondary end point in a number of clinical trials of α-blockers and finasteride, the most efficacious medical treatments for BPH.[9, 10] Since they applied several QOL instruments, comparisons among drugs are difficult.[9] Evidence shows, however, that α-blockers excel over finasteride, with earlier onset of response, greater improvements in QOL, and fewer sexual side effects.[9] The combination of finasteride with an α-blocker (terazosin, doxazosin) appears to improve QOL to a similar extent as the α-blocker alone, but to a greater extent than finasteride alone or placebo.[11, 12] Finasteride's effect on QOL was most promising in patients with large prostate.[9]

Methods

Since one of the primary goals of treating men with BPH is to improve QOL, the effects different treatments have on QOL should be considered.[5, 10, 13]

Randomized clinical trials were identified through a MEDLINE search (January 1966–May 2002). An optimally sensitive search strategy[14] using the medical subject headings including all subheadings and text key words (saw palmetto, *Serenoa repens*, phytosterols, sitosterols, *Sabal serrulata*, β-sitosterols, medicine, herbal, plant extracts, plants, medicinal, quality of life, qol, ql, heath-related quality of life, hrqol). The results were limited to human studies and the English language. Similar searches were conducted in EMBASE, the Cochrane Library, ClinPSYC (1990–2001), and HealthSTAR (1975–2001). In addition, studies were identified through retrieving references cited in identified studies and review articles. Finally, a search of the Natural Medicines database was conducted. All studies that investigated phytosterols, not in combination with other herbals or dietary supplements, for treatment of BPH and that listed QOL as an end point were included in the review.

Instruments That Assess the Effects of Phytosterols on Quality of Life in Benign Prostatic Hyperplasia

In 1993 the International Consensus Committee on BPH recommended that the International Prostate Symptom Score (IPSS) questionnaire become the gold standard in assessing treatment effect on LUTS.[15] The IPSS contains the well-validated, highly reliable ($r = 0.92$, Cronbach's $\alpha = 0.86$), and responsive American Urological Association symptom index (AUASI) for BPH, which includes seven questions covering frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency, scored on a 6-point scale.[16] Although there are no standard recommendations for grading patients with mild, moderate, or severe symptoms, patients can be tentatively classified as follows: 0–7 mildly symptomatic, 8–19 moderately symptomatic, and 20–35 severely symptomatic.

Whereas symptom evaluation of BPH are standard with the IPSS, no consensus has been reached as to which QOL instrument is preferred.[10, 13, 15] Numerous instruments are available and can be divided into two categories, generic and disease specific.[17] Generic measures allow for broad comparisons of interventions across a variety of health states. The best known are the Sickness Impact Profile, the Short Form

(SF)-36, and the EuroQoL.[18–20] It is unlikely, however, that these instruments will be sensitive to changes after BPH treatment.[17] Disease-specific measures are often more sensitive, but they do not allow for cross-condition comparisons and are limited as to interventions or populations in which they can be used.[17] Disease-specific instruments for BPH are the IPSS QOL question, International Continence Society QOL (ICS-QoL), BPH Health-related QOL Short Form 9 (BPH HRQoL-9), BPH Impact Index (BPHii), and Mayo Clinic Health-related QOL (Mayo HRQoL) questionnaire.[16, 21–24]

In addition to the AUASI, the IPSS contains the following question: "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" Answers range from "delighted" to "terrible" (0–6). This question correlates well with overall symptom score and summarizes the impact of urologic symptoms.[15]

The ICS-QoL contains six questions, two addressing general issues (interference of LUTS with life, feelings about having LUTS for rest of life), three addressing symptom-related issues (need to change clothes because of incontinence, need to reduce drink intake, length of time with LUTS), and one addressing worries associated with LUTS. Each item has anywhere from four to seven possible responses. The results are reported as the proportion of patients selecting each response. The ICS-QoL has good content and construct validity, but poor internal consistency (Cronbach's $\alpha = 0.59$).[21]

The BPH HRQoL-9 investigates BPH-specific social (including sexual function) and general realms. Originally constructed as a 20-item questionnaire, a 9-item tool was developed consisting of 1-cm visual analog scales. The internal consistency was 0.70 and retest reliability was 0.7.[22]

The BPHii was developed in conjunction with the AUASI for men with LUTS. It contains four items related to physical discomfort, worry, bothersomeness, and interference with daily activities scored on a scale from 0–4. The BPHii has good internal consistency (Cronbach's $\alpha = 0.87$) and retest reliability ($r = 0.83$).[23]

The Mayo Clinic questionnaire contains 44 items in 6 domains: symptoms, bother, general health perception, BPH-specific interference with activities, worries, and concerns and sexual satisfaction. Items are scored on a scale from 0–6. Test-retest reliability was only moderate ($r = 0.41–0.43$). Cronbach's α was 0.81–0.96 for most domains, although for general health perceptions it was 0.32. The Mayo HRQoL has had only limited use in clinical trials.[24]

Problems with internal consistency, limited clinical use, high respondent burden, and narrow response options hinder the use of many of these BPH-specific measures of QOL[21–24] Inconsistent use of any one or group of QOL measures in the past makes comparison with today's data difficult.[13]

Clinical Trials

The effects of phytosterols on QOL in patients with BPH were studied in seven clinical trials,[25–31] four with *S. repens*[25–28] and three with β-sitosterols (Table 1).[29–31]

Dosages of *S. repens* were 160–320 mg/day for up to 6 months. Two trials were dose-ranging studies,[18–19] one study compared *S. repens* with finasteride,[20] and only one was placebo controlled.[21]

Trials of β-sitosterols used two standard preparations, Harzol and Azuprostat, containing 20 and 130 mg/day of β-sitosterols, respectively.[25–27] Two studies were placebo controlled,[25–27] and the third was an open-labeled extension of one of the earlier studies.[26]

Serenoa repens

In one study 305 men with untreated BPH took *S. repens* 160 mg twice/day for 3 months.[25] The IPSS QOL score was evaluated at baseline and at days 45 and 90. Although actual scores were not provided, improvements were seen at both days ($p<0.0001$). The QOL score after 45 days remained unchanged in 33% of patients, improved in 65%, and worsened in 2%. At 90 days, scores were unchanged in 19%, improved in 78%, and worse in 3% of patients.

The article is limited in the amount and quality of data reported. Whereas 65% and 78% of patients showed improvement at 45 and 90 days, respectively, what constituted improvement was not defined. Lack of a placebo-control group limits what can be learned from any clinical trial, but it is especially difficult to draw conclusions from a BPH clinical trial, since up to 45% of patients will respond to placebo. As with previous studies, this one had a limited number of patients.

A 3-month, double-blind, randomized, parallel-group study compared the efficacy and tolerability of two regimens of the lipidosterolic extract of *S. repens* (Permixon)[26] Ninety-two men aged 50 years or older with symptomatic

Table 1. Clinical Trials Assessing Phytosterols' Effects on Quality of Life in the Treatment of Benign Prostatic Hyperplasia

No. of Pts	Regimen	Condition	Duration	Results[a]
305[25]	*Serenoa repens* 160 mg b.i.d.	BPH	90 days	Improvements in QOL score ($p<0.0001$); after 45 days unchanged in 33% of patients, improved in 65%, worse in 2%; at 90 days, QOL unchanged in 19%, improved in 78%, worse in 3%.
45[26] 47	*Serenoa repens* 160 mg b.i.d. *Serenoa repens* 320 mg q.d.	BPH	3 mo	QOL improved from baseline in both regimens at 3 mo, 4.0 to 2.9 ($p<0.0001$) and 4.0 to 2.9 ($p<0.001$), respectively. Patients with at least 1 point ↓ in IPSS QOL score: 67% b.i.d. regimen, 72.4% q.d. regimen at 3 mo (p value not given). Regimens did not differ significantly on any other measure at 3 mo.
553[27] 545	*Serenoa repens* 320 mg/day Finasteride 5 mg	BPH	26 wks	QOL improved from baseline in patients receiving *Serenoa repens* for 26 wks (3.63 to 2.25, $p<0.001$). QOL improved to similar extents in *Serenoa repens* and finasteride groups ($p=0.14$). Over 50% of patients felt QOL was improved regardless of whether they received *Serenoa repens* or finasteride.
41[28] 44	*Serenoa repens* 160 mg/day Placebo	LUTS	6 mo	No significant improvement in QOL between *Serenoa repens* and placebo (-0.7 and -0.3, $p=0.20$) at 6 mo.
96[29] 91	β-Sitosterol 20 mg/day Placebo	BPH	6 mo	QOL improved at 6 mo with mean change from baseline of -1.4 and -0.2 ($p<0.01$) for β-sitosterol and placebo, respectively.
38[30] 14 12 27 18 8	G1: β-sitosterol 20 mg/day x 18 mo G2: β-sitosterol 20 mg/day x 6 mo G3: β-sitosterol 20 mg/day x 6 mo, then other phytotherapy G4: Placebo x 6 mo, then β-sitosterol 20 mg/day up to 18 mo G5: Placebo x 6 mo G6: Placebo x 6 mo, then other phytotherapy	BPH	18 mo	G1 continued to have favorable outcomes achieved in previous 6-mo trial but did not provide additional benefit with longer treatment. G4 improved to same extent as G1 for all end points examined. G1 and G4 improved all end points at 18 mo compared with those who did not receive β-sitosterol in open extension trial ($p<0.01$).
88[31] 89	β-Sitosterol 130 mg/day Placebo	BPH	6 mo	QOL score improved compared with placebo at 6 mo (-1.8 vs -0.9, $p<0.01$).

[a]All trials used the International Prostate Symptom Score (IPSS) quality of life (QOL) questionnaire.
BPH = benign prostatic hyperplasia; LUTS= lower urinary tract symptoms.

BPH for at least 6 months were randomly allocated to *S. repens* 160 mg twice/day or 320 mg once/day. Changes from baseline in IPSS QOL score were measured after 3 months. Scores improved from baseline in men receiving both dosages at 3 months (4.0 ± 0.7 to 2.9 ± 1.2, $p<0.0001$, 4.0 ± 1.0 to 2.9 ± 1.3, $p<0.001$, respectively). The percentage of patients with at least a one-point decrease in the score was 66.7% with the twice-daily regimen and 72.4% with the daily regimen at 3 months (probability not reported).

In the largest study (> 1000 patients), *S. repens* 320 mg (Permixon) and finasteride 5 mg were compared in a 6-month, randomized equivalence trial in men with moderate BPH.[27] The primary QOL end point was the IPSS question at 26 weeks. The QOL improved from baseline in patients receiving *S. repens* for 26 weeks (3.63 ± 1.28 to 2.25 ± 1.29, $p< 0.001$), with similar changes in the finasteride group (3.66 ± 1.17 to 2.15 ± 1.26, $p< 0.001$). This improvement was similar in both groups ($p=0.14$). Over 50% of patients felt their QOL was improved (> 1-point decrease in the 7-point scale) regardless of which treatment they received.

After a 1-month run-in period, 85 men aged 45 years or older with LUTS and IPSS of 8 or greater, were randomized to receive *S. repens* 160 mg twice/day or placebo for 6 months.[8] The IPSS QOL was measured at baseline and 6 months after randomization. No improvement in scores was noted between groups (*S. repens* -0.7, placebo -0.3, $p = 0.20$) at 6 months.

Potential study limitations included small sample and imperfectly matched treatment and

placebo groups. Men receiving *S. repens* had a higher (although not statistically significant) IPSS at baseline compared with placebo recipients, which may have resulted in the former being more likely to show variability regarding improvement (regression to the mean).

β-Sitosterols

Two randomized, placebo-controlled, double-blind trials evaluated β-sitosterols (Harzol).[29] The first one randomized 187 patients with symptomatic BPH to β-sitosterol 20 mg 3 times/day or placebo for 6 months. The IPSS QOL was administered at baseline and 6 months. At 6 months, IPSS QOL scores showed improvement, with a mean change from baseline of 1.4 ± 0.8 and 0.2 ± 1.0 ($p<0.01$) for β-sitosterol and placebo, respectively.

An 18-month follow-up study was an open extension of the 6-month trial and is the only one to examine the long-term effects of phytosterols on QOL in patients with BPH.[30] Men in this phase were free to choose their treatment, with 117 of the initial 305 patients opting to participate. They were reevaluated with the IPSS QOL 18 months after randomization for the first study. Those previously treated with β-sitosterol who continued the drug continued to have favorable QOL outcomes but did not receive any additional benefit from longer treatment. Men who previously received placebo and who began therapy with β-sitosterol had improvement to the same extent as the original double-blind trial treatment group. Patients who chose β-sitosterol for further therapy had significant improvements in QOL at 18 months compared with those who did not receive β-sitosterol in the open extension trial ($p<0.01$). Patients who received β-sitosterols in the double-blind trial but decided not to take any phytotherapy in the follow-up arm still had improvement over those who had never received phytotherapy ($p<0.01$). The authors concluded that the effects on QOL of β-sitosterol are maintained over at least 18 months in men with symptomatic BPH.

Another double-blind, placebo-controlled trial examined a β-sitosterol (Azuprostat) in patients with symptomatic BPH.[31] A total of 177 patients received β-sitosterol 130 mg/day or placebo once/day. After a 4-week washout period, patients were evaluated at baseline and 6 months for changes in QOL using the IPSS question. The IPSS scores improved to a greater extent in the β-sitosterol group than in the placebo group (-1.8 ± 1.02 vs -0.9 ± 0.91, $p<0.01$).

Discussion

Based on the studies reviewed, phytosterols are generally well tolerated and potentially effective in treating symptoms of BPH and in improving QOL. Of the seven studies,[25–31] six[25–27, 29–31] showed beneficial effects.

Use of herbal supplements is clearly on the rise in the United States.[32] Millions of Americans frequently include the products as part of their routine health regimens to prevent or treat disease and improve QOL.[33] Herbal supplements have been studied in both Europe and the United States to determine whether claims to improve health are justified. In many cases, such as with phytosterols for BPH, data support their efficacy.[1,4, 25–31] However, other herbals lack the support of well-conducted clinical trials.[8] Because most herbal supplements aim to improve QOL, we initially planned to review the literature that investigated the effects of the 12 most commonly used herbals in the United States.[34] This search revealed 23 studies investigating QOL as either a primary or secondary end point. Phytosterols have evidence supporting their clinical efficacy, but many herbals lacked a suitable number of studies to draw a solid conclusion. For this reason, we limited our review to the effects of phytosterols on QOL in patients with BPH.

A number of issues must be considered before drawing conclusions. First, poor design limits what can be learned from these studies. Most studies had a limited number of patients and were not powered to detect differences in QOL.[25, 26, 29, 30] Small studies often are not able to show statistical significance even when it exists.

Lack of a control group is also a confounding factor due to the large placebo effect (~45% improvement) realized in BPH clinical trials.[10] There is little evidence of phytosterol's long-term efficacy (> 6 mo) in reducing symptomatology and increasing QOL.[1,4, 25–29, 31] In addition, the agents have not been adequately compared with finasteride and lack comparison with α-blocking agents, the most widely used and effective drugs to treat BPH.[10]

Next, it is difficult in the case of the IPSS QOL question to determine what constitutes a clinically significant change compared with a statistically significant one. A number of studies considered an increase in QOL score of more

than 1 point (on a scale of 0–6) to be clinically significant.[26,27] When applied to the reviewed studies, all those with statistically significant improvements would have clinically significant improvements in QOL.[25–27, 29–31] Potential downfalls were proposed with the use of the minimal clinically important difference (MCID) for QOL measures due to inherent problems related to their calculation that may result in oversimplification of results.[35] Several issues should be considered when interpreting MCIDs, including cost of therapy and baseline QOL. A therapy that results in a statistically significant change always should be assessed in context of what it costs in terms of dollars and adverse effects. In addition, the clinical significance of a QOL change will depend on the patient's baseline assessment. When applying MCIDs to study results, these issues must be kept in mind.

We briefly reviewed a variety of BPH-specific QOL questionnaires that were applied in clinical trials. All the studies identified in this review used the IPSS QOL question. It may be that alternative questionnaires may be more accurate.

Finally, our ability to identify studies was limited by a number of factors. The National Library of Medicine does not consistently index articles on herbal supplements, so MEDLINE searches are not all-inclusive. Thus, we conducted searches for studies according to the Cochrane Database for Systematic Reviews' recommendations.[14] Additional searches of other databases were conducted, as well as reviews of references of identified studies and review articles. A second limitation to our review of the literature was exclusion of studies published in foreign languages. Herbal supplements such as phytosterols have greater acceptance in Europe than in the United States,[2] and it is possible that we missed many studies due to our inability to translate them.

Summary

It appears that phytosterols improve QOL in men with BPH.[25–27, 29–31] However, confirmatory studies that are more methodologically sound and have larger study populations are required to support these findings. Since few studies evaluated the effect of phytosterols beyond 6 months, there is little evidence of the compounds' long-term efficacy in reducing symptomatology or improving QOL.[1, 4, 25–29, 31] Phytosterols have not been adequately compared with α-blocking agents.[10] Larger studies comparing them with other treatments of BPH must be conducted. In addition, consensus as to which questionnaires should be used to evaluate potential changes in QOL after treatment of BPH symptoms remains to be reached.

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