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β-sitosterol for the treatment of benign prostatic hyperplasia: a systematic review

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Objectives To conduct a systematic review of the evidence for the efficacy of β-sitosterol in men with symptomatic benign prostatic hyperplasia (BPH).

Methods Studies were identified through Medline™ (1966–98), EMBASE™, Phytodok, the Cochrane Library, bibliographies of identified trials and review articles, and contact with study authors and pharmaceutical companies. Randomized trials were included if: men had symptomatic BPH; plant extract preparations contained β-sitosterols; a control group received placebo or a pharmacological therapy; and treatment duration was ⩾30 days. Study characteristics, demographic information, enrolment criteria and outcomes were extracted.

Results Four trials comprising a total of 519 men met the inclusion criteria. All were double-blind and lasted 4–26 weeks. Three studies used nonglucosidic β-sitosterols and one used a preparation that contained only β-sitosterol-β-D-glucoside. Compared with placebo, β-sitosterol improved urinary symptom scores and flow measures. For the two studies reporting the International Prostate Symptom Score (IPSS), the weighted mean difference (WMD) against placebo was −4.9 IPSS points (95% confidence interval, CI, −6.3 to −3.5). The WMD for peak urinary flow rate was 3.91 mL/s (95% CI 0.91 to 6.90, four studies) and for residual volume the WMD was −28.62 mL (95% CI −41.42 to −15.83, four studies). β-sitosterol did not reduce prostate size. The trial using pure β-sitosterol-β-D-glucoside (WA184) showed no improvement in urinary flow measures. Withdrawal rates for men assigned to β-sitosterol and placebo were 7.8% and 8.0% (not significant), respectively.

Conclusion β-sitosterol improves urological symptoms and flow measures. However, the existing studies are limited by short treatment duration and lack of standardized β-sitosterol preparations. Their long-term effectiveness, safety and ability to prevent the complications of BPH are unknown.

Keywords β-sitosterol therapy, plant extracts, benign prostatic hyperplasia (BPH), meta-analysis

Introduction

LUTS attributable to BPH are one of the most common medical conditions in older men. Histological evidence of BPH is found in > 40% of men in their 50s and nearly 90% of men in their 80s [1]. For a 50-year-old man the estimated lifetime chance of requiring therapy is 40% [2]. The treatment goal in the vast majority of these men is to relieve bothersome obstructive and irritative symptoms. In the USA, the treatment of BPH costs $2 billion, accounts for 1.7 million physician office visits [3] and results in over 100 000 prostatectomies annually [4].

There is a wide variety of options for the treatment of symptomatic BPH, including lifestyle modification, medical, surgical and device therapies. The standard treatment, especially for men with severe symptoms or complications resulting from prostatic obstruction, has been TURP. Pharmacological therapies, such as 5α-reductase inhibitors and α-adrenergic receptor blockers, have also been shown to effectively reduce urinary symptoms and improve urinary flow measurements [5]. In addition, 5α-reductase inhibitors have been shown to reduce the development of acute urinary retention or need for surgery in men with moderate BPH symptoms who have enlarged prostates [6].

Extracts of plants and herbs have been used for medicinal purposes (phytotherapy) since ancient times. Presently, the sale of all botanical medications in the USA is $1.5 billion per year [7,8]; worldwide, the sale of plant extracts for the treatment of BPH is ≈$80 million per year [9]. Phytotherapeutic agents represent nearly half of the medications dispensed for the treatment of BPH in Italy, compared with 5% for α-blockers and 5% for 5α-reductase inhibitors [10]. In Germany and Austria, phytotherapy represents > 90% of all drugs

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prescribed for the treatment of BPH [11]. In the USA, they are readily available as nonprescription supplements to ensure prostate health and are often recommended as a 'natural treatment' for BPH symptoms. Nearly a quarter of men seen with previously treated BPH at a university urology clinic for urinary symptoms indicated they had used phytotherapeutic agents [12].

There are about 30 phytotherapeutic compounds used in the treatment of BPH, including those that contain β-sitosterols [13]. β-sitosterol is a phytopharmacological extract containing a mixture of phytosterols, with smaller amounts of other sterols, bonded with glucosides. These phytosterols are commonly derived from the South African star grass, *Hypoxis rooperi*, or from species of *Pinus* and *Picea*. The purported active constituent is termed β-sitosterol. Additionally, the quantity of β-sitosterol-β-D-glucoside is often reported. Although the exact mechanism of action of β-sitosterols is unknown it may be related to cholesterol metabolism or anti-inflammatory effects (via interference with prostaglandin metabolism) [14].

The aim of this study was to provide a comprehensive overview including a quantitative meta-analysis of the existing evidence to determine the therapeutic efficacy and safety of compounds containing β-sitosterols. We specifically intended to determine if preparations containing β-sitosterols are more effective than placebo, and comparable with pharmacological therapy in improving urinary symptoms and/or measurements in men with BPH. We also assessed the safety and tolerability of β-sitosterol preparations.

Methods

Inclusion criteria

Studies were included in the review if they met the following criteria: men had symptomatic BPH, the treatment intervention contained β-sitosterol (also termed Harzol, Azuprostat, WA184) alone or in combination with other phytotherapeutic agents; a control group received either placebo or pharmacological therapies; the treatment duration was $\geqslant 30$ days; and study participants were randomly assigned to treatment or control groups. Studies that used quasi-random methods of allocation, such as alternation, were excluded.

Identification of relevant trials

Medline® was searched for 1966–98 using a combination of the March 1996 update of the optimally sensitive search strategy for trials from the Cochrane Collaboration with the MeSH headings 'prostatic hyperplasia', 'phytosterols', 'plant extracts', 'sitosterols', 'Harzol', 'Azuprostat' and 'WA184', including all subheadings [15]. EMBASE for 1974–98 (performed in July 1998) was searched using a similar approach. We also searched the private database Phytodok, Munich Germany, and the Cochrane Library, including the database of the Cochrane Prostate Review Group and the Cochrane Field for Complementary Medicine. Reference lists of identified trials and reviews were searched and expert relevant triallists were asked to identify additional published or unpublished trials. There were no language restrictions.

Data extraction and study appraisal

Study characteristics, demographic information, enrolment criteria, outcomes, adverse effects and reasons for withdrawal were extracted independently by two reviewers. Missing or additional information was sought from authors/sponsors. Extracted data were reviewed by the principal reviewer and discrepancies resolved by discussion.

The main outcome was the efficacy of preparations of β-sitosterol vs placebo or active control in improving urological symptom scale scores. Secondary outcomes included peak (Q_{max}) and mean urinary flow rate, post-void residual urine volume (PVR) and prostate size.

The quality of concealment of treatment allocation was assessed as a measure of overall study quality, according to a scale developed by Schulz *et al.* [16], assigning 1 to the poorest quality and 3 to the best. Thus, 1 = trials in which concealment was inadequate (e.g. such as alternation or reference to case record numbers or to dates of birth); 2 = trials in which the authors either did not report their approach to concealing allocation or reported an approach that did not fall into one of the other categories (e.g. studies noting 'randomization' or 'random allocation' but with no details about concealment method); and 3 = trials deemed to have taken adequate measures to conceal allocation (e.g. central randomization, numbered or coded containers, drugs prepared by the pharmacy, and serially numbered, opaque, sealed envelopes, etc.). Additionally, we assessed whether study participants and investigators were unaware of the treatment provided.

Statistical methods

A random-effects model was used to combine data for all outcomes. For continuous variables, weighted mean differences and their 95% CI were calculated using RevMan 3.0 software (Update Software, Oxford, UK). The difference between treatment means and their correlated SE of the difference were calculated using the methods of Lau [17] and Laird and Mosteller [18]. Papers

reported only the mean values before and after β-sitosterol therapy and control, as well as the corresponding SEM. Because the SE of the difference between the means (β-sitosterol and control) was not reported, analyses were carried out for three different assumed values of correlation (0.25, 0.50, 0.75). This approach was taken to test the sensitivity of the results to this unknown parameter. Because there were no statistically significant differences in the outcomes according to the different correlation coefficients SEMS were used, calculated with a correlation coefficient of 0.50. Chi-square tests were used to assess bivariate comparisons. Additional sensitivity analyses were performed by excluding the only study that used a compound containing pure β-sitosterol-β-D-glucoside as its β-sitosterol.

Results

The combined search strategies identified six reports of trials [19–24]. All studies were placebo-controlled and included men with mild to moderate symptomatic BPH. Four studies met the inclusion criteria [19–22]. One study was excluded for lack of clinical data [23] and one because it was an additional report of a previous publication [24]. Studies used purified extracts from a variety of plant species. Three studies contained nonglucosidic β-sitosterol, but the dosages ranged from 60 to 195 mg/day [19,20,22]. Two studies used a preparation (Azuprostat) that contained $\geqslant$ 70% nonglucosidic β-sitosterol [20,22] and one used a preparation with a nonglucosidic β-sitosterol concentration of 50% (Harzol) [19]. One study used a preparation that contained pure β-sitosterol-β-D-glucoside (WA184) [21]; in the three other trials, the quantity of this derivative was $<$ 5% of the daily β-sitosterol [19,20,22]. A total of 519 participants were randomized in the four trials.

Table 1 provides a description of the individual studies; the mean (range) age of the participants was 65.4 (34–85) years; trials lasted 4–26 weeks. The overall rate of withdrawal or losses to follow-up was 7.9% (41/519). Treatment allocation concealment was rated as unclear in three trials [20–23] and adequate in one [19]; all studies were double-blinded. Table 2 shows the baseline and outcome data from the individual studies for urological symptoms in three, Q_{max} in four, PVR in four and prostate size in two. The mean baseline values for these variables did not differ by treatment, with an IPSS of 15.2 points (n = 377), a Q_{max} of 10.2 mL/s (n = 519), a PVR of 73.3 mL (n = 519) and a prostate size of 49.1 mL (n = 262). All three studies that used preparations containing nonglucosidic β-sitosterol reported significant improvements in urinary symptoms, Q_{max} and PVR in men receiving β-sitosterol compared with placebo. The single study that used a purified β-sitosterol-β-D-glucoside preparation reported no improvement in Q_{max}, PVR or prostate size.

Weighted mean differences (WMDs) in outcome

For urinary symptoms, summary treatment effect sizes were determined for men treated with β-sitosterols or placebo. The results indicate that treatment with β-sitosterol improved urological symptoms compared with placebo (Table 3). The WMD vs placebo was −4.9 IPSS points (35% improvement vs placebo; 95% CI −6.3 to−3.5, two studies). For the Boyarsky quality-of-life score, the WMD was −4.5 points (31% improvement; 95% CI −6.0 to−3.0, one study) [19].

For urinary flow measures and prostate size, β-sitosterol was superior to placebo in improving peak (Table 3, 45% improvement) and mean urinary flow rates, and PVR. When excluding the study that used only WA184 [21], the WMD for the Q_{max} was 5.13 mL/s (53% improvement; 95% CI 2.37 to 7.89, three studies). The WMD for mean urinary flow for β-sitosterol vs placebo was 2.60 mL/s (47% improvement; 95% CI 1.30 to 3.90, one study) [19]. The PVR showed a 29% improvement (Table 3); when excluding the study that used WA184 [21], the WMD for the PVR was −29.97 mL (46% improvement; 95% CI−38.27 to−21.66, three studies). β-sitosterol did not significantly reduce prostate size; the WMD for prostate size was −6.19 mL vs placebo (4.5%; 95% CI −15.29 to 2.92, two studies).

Adverse effects caused by β-sitosterol were generally mild and comparable in frequency to those with placebo; the withdrawal rates were 7.8% with β-sitosterol and 8.0% with placebo (not significant). Gastrointestinal side-effects were the most common, occurring in 1.6% of men on β-sitosterols and in none taking placebo. Impotence was reported in 0.5% of men on β-sitosterols; no men randomized to placebo reported impotence.

Discussion

This is the first systematic review summarizing the evidence from randomized controlled trials for the efficacy and safety of β-sitosterols in men with LUTS attributable to BPH. The available data suggest that β-sitosterols improve urinary symptoms and flow measures, and are associated with few adverse events. Compared with placebo, β-sitosterols improved urinary symptom scores by 35%, Q_{max} by 34%, mean urinary flow rate by 47% and PVR by 24%.

The baseline characteristics of the participants (age, prostate volume, Q_{max} and symptom scores) were comparable with those in previous trials and meta-analyses involving the pharmacological management of BPH [25]. The treatment effect size on the urological symptoms

Table 1 Description of the individual studies

Characteristic	*Study reference* [19]	[20]	[21]	[22]
Details of participants	SBPH	SBPH	SBPH	SBPH, IPSS ⩾6 BPH, on DRE
Q_{max}, mL/s	<15	⩾20	-	<15
at a voided volume of (mL)	⩾150	⩾100	-	⩾150
PVR (mL)	⩾30 at 150	-	-	⩾30 at 150
Mean (range) age, years	65 (50–80)	64 (34–85)	67 (53–81)	65 (53–81)
	Multicentre	-	Single centre	Multicentre
Intervention (dose × daily)	1. Harzol 20 mg × 3	1. Azuprostat M 65 mg × 3	βDG 0.15 mg × 2	1. Azuprostat M 65 mg × 3
β-sitosterol content	10 mg	⩾45 mg (70%)	-	⩾45 mg (70%)
βDG content	0.1 mg	<5%	100%	<5%
	2. Placebo	2. Placebo	2. Placebo	2. Placebo
Follow-up (weeks)	26	4	24	26
Total randomized (no. lost after randomization)	200 (10)	80 (0)	62 (9)	177 (22)
Quality of concealment of allocation*	3	2	2	2

*1 = trials in which concealment was inadequate; 2 = unclear: trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories; or study was noted to be 'randomized' or used 'random allocation' but no details were provided. 3 = trials deemed to have taken adequate measures to conceal allocation. SBPH, symptomatic BPH; βDG, β-sitosterol-β-D-glucoside.

and flow are considered clinically relevant and similar to effects reported with other pharmacological agents in placebo-controlled trials [26,27]. Reported adverse effects were infrequent and mild, and the withdrawal rate was <8%.

Methodological issues

While all studies used a double-blind method, the quality of concealment of the treatment allocation was deemed adequate in one trial [19] and unclear in three [20–22]. Studies used different doses and preparations of β-sitosterol; to date, standardized doses and preparations of β-sitosterols have not been clearly established. Although β-sitosterol is purportedly the active component, this has not been confirmed. The only study that used pure β-sitosteryl-β-D-glucoside showed no improvement in urinary flow measures and reported no information on LUTS.

The treatment duration was short, with no studies lasting longer than 26 weeks. Additionally, fewer than 600 men were evaluated. Therefore, the long-term efficacy and safety of β-sitosterol, or its effectiveness in preventing complications from BPH, e.g. acute urinary retention or the need for surgical interventions, is unknown. Furthermore, only two studies reported results from standardized and validated urological symptom scales [19,22]. Secondary outcomes were available from most but not all studies. Combining studies that used plant extracts containing different dosages of β-sitosterols may be problematic. However, if an overall quantitative estimate is deemed useful, a random-effects model that incorporates the between-study heterogeneity is appropriate, as used here.

The cost of a 90-day supply of finasteride or terazosin (5 mg/day) is ≈$200 and $120, respectively, while the cost of β-sitosterol is ≈$45 [28]. However, the costs of the initial medication may not reflect the total charges incurred for the treatment of BPH-related conditions. Previous reports have shown that finasteride can reduce the need for surgical intervention in about 6% of men who have large prostates and moderate to severe symptoms [6]. The comparative total cumulative costs of medical management alone, surgical management alone, and a combination of medicine and surgery when the initial medical management fails (mixed therapies) has been shown to depend on the age of the patient at the onset of therapy and the avoidance of mixed therapies [29]. Evaluations have not considered plant extracts nor assessed symptom relief, quality of life or performed cost-effectiveness analyses. However, medical management (including plant extracts) in younger patients appears to be costly over time unless it can also reduce urinary retention or the need for surgery. The modest decreases in the already low rates of retention and prostatectomy after 2 years of treatment with 5α-reductase inhibitors do not appear to justify the costs. In men with mild to moderate symptoms of BPH that do not interfere with

Table 2 A summary of outcome data for symptom scores, prostate size, peak urinary flow and residual volume; β-sitosterols vs control

Study Ref	*Mean (SD)‡ Symptom scores* *β-sitosterol*	*Control*	*Q_{max}, mL/s* *β-sitosterol*	*Control*	*PVR, mL* *β-sitosterol*	*Control*	*Prostate size, mL* *β-sitosterol*	*Control*
[19]	IPSS							
Baseline	14.9 (4.7)	14.9 (3.7)	9.9 (2.5)	10.2 (2.8)	65.8 (20.8)	64.8 (23.5)	44.6 (19.4)	48.0 (27.9)
Follow-up	7.7 (4.2)	12.2 (3.9)	15.2 (5.7)	11.4 (4.7)	30.4 (39.9)	54.3 (27.6)	42.3 (18.2)	48.8 (26.5)
Difference	−7.2	−2.7*	5.3	1.2*	−35.4	−10.5*	−2.3	0.8
[20]								
Baseline	†	-	10.7 (3.1)	12.3 (3.3)	84.0 (24.3)	78.0 (26.2)	NA	
Follow-up	-	-	23.1 (6.0)	14.7 (5.6)	37.5 (23.9)	74.8 (34.5)		
Difference	(a) 82.5% (b) 82.5%	(a) 7.5%† (b) 10.0%†	12.3	2.3 *	−46.5	−3.2*		
[21]								
Baseline	NA	-	9.9 (2.7)	7.6 (2.6)	123.0 (92.6)	150.0 (101)	56.3 (25.5)	62.5 (25.4)
Follow-up	-	-	10.8 (0.3)	10.4 (0.3)	144.0 (86)	103.0 (83)	57.1 (24.5)	62.1 (29.9)
Difference	-	-	0.9	2.8	21.0	−47.0	0.9	−0.4
[22]	IPSS							
Baseline	16.0 (4.6)	14.9 (5.2)	10.3 (3.3)	11.3 (2.7)	63.4 (29.0)	63.1 (26.4)	NA	
Follow-up	7.8 (4.9)	12.1 (5.6)	19.4 (8.6)	15.7 (6.1)	25.6 (28.8)	59.1 (44.1)		
Difference	−8.2	−2.8*	9.1	4.4*	−37.8	−4.0*		

‡ (if provided); *$P<0.05$ † Patient/physician overall evaluation of efficacy considered very good or good (vs satisfactory or bad) by (a) the patient or (b) the physician; differences in efficacy ($P<0.001$).

Table 3 Weighted mean differences (WMD) in peak urinary flow rates and residual volume for men treated with β-sitosterols vs placebo. Negative values of the WMD favour placebo for Q_{max} and β-sitosterol for PVR

Variable	*Study Ref [19]*	*[20]*	*[21]*	*[22]*	*Total*
Q_{max}, mL/s					
Experimental no.	95	40	25	77	237
Mean (SD)	15.2 (6.43)	23.1 (7.08)	10.75 (3.50)	19.4 (9.21)	-
Control no.	91	40	28	78	237
Mean (SD)	11.4 (6.30)	14.7 (7.08)	10.37 (3.70)	15.7 (9.27)	-
Weight (%)	27.1	22.8	26.7	23.4	100
WMD (95% CI)	3.8 (1.97, 5.63)	8.4 (5.30, 11.50)	0.38 (−1.56, 2.32)	3.7 (0.79, 6.61)	3.9 (0.91, 6.90)
PVR, mL					
Experimental no.	96	40	25	77	238
Mean (SD)	30.4 (43.31)	37.5 (39.40)	144.0 (125.80)	103.0 (133.13)	-
Control no.	91	40	28	78	237
Mean (SD)	54.3 (42.16)	74.8 (39.40)	25.6 (47.30)	59.1 (47.60)	-
Weight (%)	37.2	27.8	3.2	31.9	100
WMD (95% CI)	−23.9 (−36.15,−11.65)	−37.3 (−54.57,−20.03)	−41.0 (−28.74, 110.74)	−33.5 (−48.44,−18.56)	−28.6 (−41.42,−15.83)

lifestyle, watchful waiting remains a good initial option [30].

Additional placebo and active-controlled studies are needed. These trials should use standardized extracts with known concentrations of β-sitosterol. Future trials should be of sufficient size and duration to detect important differences in outcomes, including urological symptom scale scores (e.g. the IPSS), mean and peak urinary flow rate, voided volume, prostate size, PVR, development of acute urinary retention or need for surgical intervention. Studies are needed to compare β-sitosterols, α-blockers, 5α-reductase inhibitors and other phytotherapeutic agents, such as *Serenoa repens* (saw palmetto plant extract) [31,32]. Additionally, cost-effectiveness studies should be conducted to evaluate the long-term cumulative costs associated with plant extracts, including the potential need for surgical intervention.

Until the results of these studies are available, this systematic review provides the most complete assessment of the efficacy and safety of β-sitosterols in the treatment of mild to moderate BPH. The available evidence suggests that β-sitosterols are well tolerated and improve urological symptoms and flow measures. The long-term effectiveness and safety of β-sitosterols and their ability to prevent complications from BPH are unknown.

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Editorial comment

I congratulate the authors on this systematic review of β-sitosterol; this agent is reported to have the greatest efficacy amongst 'phytotherapeutic' substances. This objective and scientifically based review from the Cochrane Collaborative Review Group provides a clear picture of sitosterols based on the current literature. In particular, this study emphasizes that different preparations containing different concentrations of β-sitosterol have been used in previous studies at varying dosages. Based on the information provided from this review, it would appear that β-sitosterols have a similar efficacy to α-adrenergic antagonists and a comparative study of β-sitosterol with comtemporary α-antagonists would seem the logical next step. A major concern with the existing data is that the duration of treatment is short, with none of the studies having lasted for >26 weeks and in total fewer than 600 men have been evaluated to date. Contributions such as this paper provide an extremely important tool in our search for evidence-based practice and emphasize the importance of systematic reviews using the Cochrane principles. This approach clearly emphasizes the strengths and weaknesses of the existing literature, as assessed using clinically based meta-analyses.

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