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Are D-mannose Pills an Effective Form of Prophylaxis for Women Prone to Recurrent Urinary Tract Infections?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not are D-mannose pills an effective form of prophylaxis for women prone to recurrent urinary tract infections?

Study Design: Systematic review of three randomized controlled trials (RCTs) published between 2014-2016, all in the English language.

Data Sources: Three randomized controlled trials (RCTs) which evaluated the effectiveness of D-mannose as prophylaxis against recurrent UTI in women as compared to control groups either given no prophylaxis and or antibiotic prophylaxis. All studies were found using PubMed and the Cochrane library.

Outcomes Measured: All three studies measured the number of patients that had a recurrent UTI during the follow-up period. One study also measured the time to recurrence of UTI and change in pain and urgency symptoms on the visual analog scale (VAS).

Results: All three studies found that patients were significantly less likely to have a UTI recurrence with D-mannose compared to no agents for prophylaxis. One study found similar efficacy of D-mannose and nitrofurantoin for prophylaxis; however, tolerability of D-mannose was significantly better than that of nitrofurantoin. A third study found that D-mannose prevented urinary tract infections better than trimethoprim-sulfamethoxazole (TMP-SMX), however, dosing of TMP-SMX was suboptimal.

Conclusions: D-mannose was found to be effective in preventing recurrence of urinary tract infections in women prone to such infections. Further studies are needed to determine optimal dosing of D-mannose for prophylaxis. In addition, more studies conducting an adequate comparison of D-mannose to conventional antimicrobial therapy are required before implementing this supplement as standard of care.

Key Words: D-mannose, Urinary Tract Infection, Recurrent UTI

INTRODUCTION

A urinary tract infection (UTI) is a bacterial infection of the urinary tract that either manifests as cystitis or migrates up the urinary tract into the kidney and causes pyelonephritis. UTI is one of the most common infections occurring in females worldwide.[1] Recurrent urinary tract infection is defined as two culture-proven infections in 6 months or 3 in 12 months.[1,2]. UTIs are most commonly caused by *E. coli*. Other less common pathogens include *S. saprophyticus*, *Klebsiella pneumoniae,* and *Proteus mirabilis.*[1] The condition is more common in females due to anatomic features allowing easy ascent of fecal flora into the urinary tract. Recurrent urinary tract infections can occur from persistence of bacteria after treatment of initial infection either due to inadequate treatment, noncompliance, or high organismal counts. Recurrent infections can also occur from recolonization of the urinary tract. Some patients may be predisposed to recurrent UTI due to structural or functional abnormalities.

It is estimated that worldwide, nearly 150 million UTIs occur annually.[3] The lifetime risk of a female getting a UTI is 50%.[1] About 36% of women younger than 55 and 53% of women over 55 report recurrence in one year.[1] Urinary tract infections are projected to cost over $6 billion annually[3] and account for nearly 7 million office visits per year.[4] A retrospective analysis in Europe estimates a mean annual cost of $270 per patient for a UTI. This cost includes the physician visit, diagnosis, and treatment of the condition.[5] In addition to economic burden, urinary tract infections, especially recurrent infections, are known to cause significant painful symptoms and psychological distress in women.

Uncomplicated UTI is often treated with trimethoprim-sulfamethoxazole (TMP-SMX), nitrofurantoin, ciprofloxacin, or cephalexin for 3-10 days depending on the selected therapy and the patient. Recurrent UTI is treated with nightly or post-coital prophylaxis with TMP-SMX or

nitrofurantoin. With the increasing advent of antibiotic resistance and adverse effects from frequent or daily antibiotic use, alternative methods are necessary for preventing recurrent UTI, a common, devitalizing condition.

D-mannose is a simple, natural sugar that inhibits bacterial adhesion to the urothelium.[6] Bacterial fimbriae preferably bind D-mannose in the urine rather than proteins on the bladder wall.[6] Once bound, this complex is trapped in the urine and eliminated during urination and therefore the bacteria cannot cause infection. This mechanism is especially relevant for the most common UTI pathogen, *E. coli*, which exerts its virulence by attaching its fimbriae to the urothelium to persist and proliferate in the urinary tract.[1] D-mannose has been reported to relieve lower urinary tract symptoms and prevent recurrence of UTI in women prone to the condition without the use of antimicrobial therapy.[6] This paper evaluates 3 randomized, controlled trials (RCTs) evaluating the efficacy of D-mannose for prophylaxis against recurrent UTI in females prone to this condition compared with no prophylactic therapy and conventional antimicrobials.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not are D-mannose pills an effective form of prophylaxis for women prone to recurrent urinary tract infections?

METHODS

This systematic review uses three randomized controlled trials (RCTs). All articles were researched using the Cochrane library and PubMed. Articles selected displayed relevance to this topic and were required to study outcomes that were POEMs (patient-oriented evidence that matters). These articles were found using keywords "D-mannose", "urinary tract infection", and "women". All three articles were published in peer-reviewed journals, and all were published in English. Articles were published no earlier than 2007. Any studies using male subjects or

subjects under age 18 were excluded. See Table 1 for inclusion and exclusion criteria specific to each of the studies used in this review.

Table 1. Demographics and Characteristics of Included Studies

Study	Type	# pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Domenici, 2016[6]	RCT	45	18-65	Women age 18-65 years, symptoms of acute cystitis, asymptomatic with diagnosis of a UTI (10^3 or more colony-forming units per mL)	History of urinary tract anomaly, acute symptoms >1 week, pregnant/breast feeding, trying to conceive, inflammatory UTI, hormone replacement, interstitial cystitis, DM, catheter use, previously antibiotic prophylaxis, unable to fill out questionnaire	2	D-mannose 1 week per month, every other month for 6 months No treatment
Kranjcec, 2014[2]	RCT	308	29-58	Female Age > 18 yrs Positive history of recurrent cystitis	Pregnancy, breast feeding, symptoms of upper UTI, symptoms of inflammatory response, history of urinary tract anomalies, interstitial cystitis, DM, use of hormone therapy or contraception, previously had UTI prophylaxis	0	2 g D-mannose QHS No prophylaxis
Porru, 2014[7]	RCT	60	22-54	Female >18 yrs, acute symptomatic UTI, ≥ 3 UTIs w. positive urine cultures in the last 3 months, no antimicrobials within 4 weeks, not pregnant/contemplating pregnancy	Upper UTI and/or temperature > 38˚ C, flank/lumbar pain, renal disease, anatomic abnormalities, prior GYN surgery, immunosuppressive medications or diseases	0	D-mannose 3 g TID x 2 weeks then 1g BID x 22 weeks TMP-SMX 160/800 mg BID x 5 days then QHS for 23 weeks

The population studied involved women over age 18 with history of recurrent urinary tract infection, defined as 3 or more culture-proven urinary tract infections in 12 months. The intervention being studied is D-mannose pills for prophylactic therapy against recurrent UTI. Comparison in one study was no prophylaxis. The second study had two control groups: one given prophylaxis with nitrofurantoin and one given no prophylaxis. The third study used one control group given prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX). The major outcome measured in these studies was whether or not the patient reported irritative voiding symptoms consistent with the onset of an acute, recurrent UTI. Two of the studies confirmed the reported infection with a urine culture to verify that symptoms were consistent with a true UTI recurrence.

Data analysis of this study was conducted using the number of patients in each group reporting urinary symptoms after initiation of the prophylactic regimen. One study also recorded mean time to recurrence with standard deviation values as well as urinary pain and urgency on the visual analog scale (VAS). Statistical analyses used include p-value, risk reduction, and 95% confidence intervals.

OUTCOMES MEASURED

The studies measured the number of patients with a recurrence of UTI by patient-reported irritative voiding symptoms. These symptoms included dysuria, frequency, urgency, nocturia, hematuria, suprapubic pain, and low back pain. Kranjcec et al. and Porru et al. confirmed UTI onset with a urine culture after patients reported symptoms. Porru et al. also recorded the mean time to recurrence (TTR) of the UTI with standard deviation, and patient-reported pain and urinary urgency on the visual analog scale (VAS) with standard deviation.

RESULTS

Three RCTs were used to determine whether D-mannose is an effective agent for prophylaxis against recurrent UTI. Each of the studies compared D-mannose use with no prophylactic therapy or other conventional prophylactic methods. Prior to initiation of prophylaxis, all studies enrolled patients with acute cystitis; patients were treated as described later. In two studies, subjects were considered cured if they reported resolution of symptoms and had a negative urine culture. The third study considered patients cured if they did not report persistence of symptoms after treatment. The focus of this review is on the follow-up period after treatment and cure of acute cystitis when subjects were monitored for recurrence of UTI while using D-mannose for prophylaxis or other methods. Refer to Table 2 for comparison of recurrence of UTI in women with varying interventions in all RCTs.

Table 2. Number of patients having a recurrent UTI across all 3 RCTs

Group	Number of Patients having recurrence of UTI	P-value	Numbers needed to treat (NNT)
Domenici et al.			
D-mannose	1 (4.5%)	P < 0.05	4
No prophylaxis	7 (33.3%)		
Krancjec et al.			
D-mannose	15 (14.5%)	P < 0.001	3
No prophylaxis	62 (60.7%)		
Porru et al.			
D-mannose	12 (20%)	P < 0.0001	2
TMP-SMX	45 (75%)		

Domenici et al. studied women with acute cystitis or asymptomatic culture-proven UTI and a history of recurrent UTI. Subjects were treated for acute UTI with D-mannose 1.5 g twice per day for 3 days and then once daily for 10 days. Patients were considered cured if they

reported symptom cure according to the Urinary Tract Infections Symptoms Assessment (UTISA). This was confirmed with urine culture. Cured subjects were then split into two groups for prophylaxis. Twenty-two subjects received D-mannose 1.5 g once a day for 1 week every other month for 6 months and 21 women received nothing. A statistically significant difference between the groups was observed. In the treatment group, 1 (4.5%) had a recurrence, while in the control group 7 (33.3%) had recurrence, $P<0.05$.[6] This study showed a large treatment effect with NNT equal to 4.

Kranjcec et al. studied women who had acute cystitis and a history of recurrent UTI. Patients were considered to have an acute infection if they reported at least two irritative voiding symptoms. This was confirmed with a positive urine culture defined as $>10^3$ CFU in a clean-catch specimen. Initial UTI was treated with ciprofloxacin 500 mg daily for 7 days and cure was defined as no lower urinary tract symptoms (LUTS) and $<10^3$ CFU on urine culture. Patients were then randomized to three groups and monitored for 6 months. The first group received 2 g D-mannose once daily at night. The second group was given nitrofurantoin 50 mg once daily at night. The third group was given nothing. If a patient reported LUTS during the follow-up period, she was said to have a recurrence, but urine culture was also performed.[2]

In the D-mannose group, 15 (14.5%) reported recurrence. In the nitrofurantoin group, 21 (20.3%) reported recurrence. In the group receiving no prophylaxis, 62 (60.7%) reported recurrence. The number of recurrent episodes was statistically different between the group with no prophylaxis and those with either D-mannose or nitrofurantoin ($P< 0.001$). Risk reduction (RR) of recurrent cystitis episode in the D-mannose group compared with the no prophylaxis group was 0.239 and was statistically significant (95% CI 0.146-0.392, $P <0.0001$). Risk reduction of nitrofurantoin and no prophylaxis was 0.335 and statistically significant (95% CI

0.222-0.506, P<0.0001). D-mannose showed a large treatment effect compared to no prophylaxis with NNT equal to 3. Importantly, this study shows a decreased risk of recurrence with D-mannose than nitrofurantoin as reported in Table 3, but these two values may not be statistically different.[2]

Table 3. Risk Reduction of Recurrent Cystitis D-mannose vs Nitrofurantoin

Intervention	RR	95% CI	P-value
D-mannose	0.239	0.146-0.392	P < 0.0001
Nitrofurantoin	0.335	0.222-0.506	P < 0.0001

Porru et al. studied females with acute cystitis and a history of three or more documented UTIs in the last year. One group was treated with trimethoprim-sulfamethoxazole (TMP-SMX) 160/800 mg twice a day for 5 days then once daily at night for one week of each month for 23 weeks. The second group was treated with D-mannose 1 g three times a day for 2 weeks then 1 g twice daily for 22 weeks. At the end of the 24-week period, the subjects switched groups and were studied for an additional 24 weeks. Subjects were considered to have recurrence if new symptoms arose. In the D-mannose group, 12 (20%) had a UTI recurrence, while in the TMP-SMX group, 45 (75%) had a recurrence. This study showed a large treatment effect with D-mannose with NNT equal to 2. Under D-mannose mean TTR was 200 days (SD 50.7) and under TMP-SMX, mean TTR was 52.7 days (SD 11.2) and the difference was statistically significant (p<0.0001).[7] Refer to Table 4.

Table 4. Time to Recurrence of UTI TMP-SMX vs D-mannose

Group	Mean Time to Recurrence	SD	P-value
D-mannose	200 days	50.7	P < 0.001
TMP-SMX	52.7 days	11.2	

Secondarily, Porru et al. recorded patients' descriptions of their pain and urgency on the visual analog scale (VAS). Prior to D-mannose treatment mean VAS pain was 4.4 (SD 1.1) and after treatment was 2.2 (SD 0.5). Mean VAS urgency before D-mannose was 4.6 (SD 1.1) and after was 2.6 (SD 0.7). These differences were statistically significant ($p<0.001$). Refer to Table 5. VAS differences were not reported for the TMP-SMX group. However, this shows that D-mannose not only prevents recurrence, but gives patients an improved sense of symptoms and irritation from recurrent infection. This is an important component for evaluating effectiveness of prophylactic therapy given the known psychologic distress caused by recurrent UTIs.[7]

Table 5. VAS Pain and Urgency Before and After Treatment with D-mannose

	VAS Pain	**VAS Urgency**	**P-value**
Before Treatment	4.4 (SD 1.1)	4.6 (SD 1.1)	P < 0.001
After Treatment	2.2 (SD 0.5)	2.6 (SD 0.7)	

Adverse effects were reported by Krancjec et al. During the 6-month follow-up period, 37 out of 206 patients (17.9%) reported side effects, but none were severe enough to warrant stopping therapy. In the D-mannose group, 8 patients (7.8%) reported diarrhea. No other side effects were reported in this group. In the nitrofurantoin group, 29 patients (28%) reported side effects. Of these, 10 reported diarrhea, 6 reported nausea, 3 headache, 1 skin rash, and 9 vaginal burning. See Table 6. Patients in the D-mannose group had a lower risk of side effects compared to nitrofurantoin and the difference was statistically different (RR 0.276, 95% CI 0.132-0.574, P < 0.0001).[2] See Table 7. Domenici et al. had no reported side effects during treatment or prophylaxis with D-mannose.[6] Porru et al. make no mention of adverse effects.[7]

Table 6. Number of Patients with Adverse Effects of Prophylaxis

Adverse Effect	D-mannose group (number of patients reporting)	Nitrofurantoin (number of patients reporting)
Diarrhea	8	10
Nausea	0	6
Headache	0	3
Skin Rash	0	1
Vaginal Burning	0	9

Table 7. Risk reduction for side effects D-mannose compared to Nitrofurantoin

RR	95% CI	P-value
0.276	0.132-0.574	P < 0.0001

DISCUSSION

Recurrent urinary tract infections are a costly part of healthcare in the United States. In addition, these infections cause significant distress in affected women. Adequate prophylaxis measures that are both safe and effective are necessary to prevent continued recurrence of infection. Further, the advent of antibiotic resistance and the limited options for treating UTIs necessitate a safe and natural approach to preventing recurrent UTI. The primary objective of this systematic review was to evaluate the effectiveness of D-mannose as prophylaxis against UTI recurrence. Briefly explored, were patients' impressions of their relief of common symptoms of UTI, and safety and tolerability of D-mannose.

Each of the studies had limitations that must be addressed. First, none of the studies were blinded. Domenici et al. and Krancjec et al. did not offer placebo to patients receiving no prophylaxis. Further, Porru et al. employed a crossover study that had different dosing regimens for the interventions used, making it easy to tell that the two treatments were different. Randomized, double-blinded studies should be pursued to better evaluate the effectiveness of D-

mannose for prophylaxis against recurrent UTI. Further, each of the studies had relatively small patient populations. Studies involving more subjects with blinding should be conducted.

An important limitation of Porru et al. is that trimethoprim-sulfamethoxazole (TMP-SMX) was given less frequently and in lesser amount than D-mannose during the 24-week follow-up period. The study shows that D-mannose can effectively prevent recurrent urinary tract infection with only 20% of patients reporting recurrence with D-mannose. However, TMP-SMX 160/800 was dosed once daily at night for one week each month for 6 months while D-mannose was dosed 1 g twice daily. This inconsistency in dosing between the two agents limits the ability to regard one superior to the other. Recommendations for prophylactic regimens with TMP-SMX have not been concretely established, but empiric prophylaxis is most commonly low-dose TMP-SMX (80/400 or 40/200) nightly for 6 months.[1] Dosing according to the current recommendation should be used for adequate comparison of the two agents.

Another limitation is that all three studies used different doses of D-mannose for prophylaxis. Domenici et al. used 1.5 g nightly one week every other month for 6 months. Kranjcec et al. used 2 g nightly for 6 months, and Porru et al. used 1 g twice daily for 6 months. There has not yet been an established standard dose for D-mannose for prophylaxis of recurrent UTI but recommendations vary from 500 mg daily to 2 g daily in single or divided doses.[2,8] Further studies should be done to investigate optimal dosage.

Regarding cost, D-mannose is an over-the-counter supplement that is not covered by insurance. However, it is an affordable over-the-counter alternative. To address tolerability, patients reported side effects that were minimal or absent in the studies, making this supplement safe and feasible for long-term use. Of note, while D-mannose is a sugar similar to glucose, it is not able to be converted to glycogen and therefore is not stored in the body.[6] Long-term use of

this product, even in high concentrations, has shown no ill effects on metabolic function.[6] Since this sugar has no effect on metabolism, its chronic use is of no concern for causing hyperglycemia, obesity, or metabolic disorders.[8] Importantly, it can be considered safe in diabetic patients or those avoiding sugars for other reasons.[8]

CONCLUSIONS

All three studies demonstrated that D-mannose is an effective prophylactic agent for recurrent UTIs in women who are prone to these infections. There was a significant difference between D-mannose and no agent for prophylaxis in two studies. D-mannose also showed a large treatment effect across all three studies. What cannot be determined from these studies is whether D-mannose is superior to nitrofurantoin or trimethoprim-sulfamethoxazole (TMP-SMX) in terms of efficacy. D-mannose shows similar efficacy to nitrofurantoin; however, it does appear superior in terms of safety and tolerability. Studies evaluating D-mannose compared to TMP-SMX using appropriate and comparable dosing of the two agents must be pursued. Further studies should investigate D-mannose for recurrent UTI prophylaxis in larger patient populations, and should seek to establish the most effective dosing regimen. Lastly, D-mannose does improve patient perception of symptoms as reported in one study, demonstrating that it may help decrease psychologic distress associated with recurrent UTI. Ultimately, D-mannose shows promise as an effective supplement that can prevent distressing recurrent UTIs, but it does require further study before becoming standard of care for all patients.

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