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Comment

Use of d-mannose in prophylaxis of recurrent urinary tract infections (UTIs) in women

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Recurrent UTIs, defined as at least two UTIs in 6 months or three UTIs in 1 year, are a significant burden for the patient and result in high costs to the health system. There are several options for preventing recurrent UTIs, including antibiotic prophylaxis, methenamin prophylaxis and topical oestrogen. The two most commonly used strategies are long-term low-dose antibiotic prophylaxis and post-coital antibiotic prophylaxis for women who have UTI associated with sexual intercourse. Large reviews have shown that antibiotic prophylaxis lasting from 6 to 12 months (or even longer) significantly reduces the number of clinical recurrences in women with recurrent UTIs, but there is no consensus on when to start the prophylaxis, on how long it should last or at which dose and schedule the antibiotic should be taken. Several prophylactic antibiotic regimens can be used with the same efficiency. The most commonly prescribed regimens are trimethoprim-sulfamethoxazole (or trimethoprim alone), nitrofurantoin, cephalexin and the fluoroquinolones at a quarter of the usual daily dose for 6 months. The downsides of long-term antibiotic prophylaxis are possible adverse reactions (although rare), costs and increasing bacterial resistance to antibiotics; therefore, alternative prophylactic agents, such as cranberry juice and probiotics have been extensively studied. One such agent is D-mannose, which is normally present in human metabolism and has an important role, especially in the glycosylation of certain proteins. The supposed mechanism of action is inhibition of bacterial adherence to urothelial cells. *In vitro* experiments have shown that D-mannose binds and blocks FimH adhesin, which is positioned at the tip of the type 1 fimbria of enteric bacteria. During bacterial colonization, FimH binds to carbohydrate-containing glycoprotein receptors on the epithelium of the urinary tract. As it is similar in structure to the binding site of urothelial glycoprotein receptors, D-mannose acts as a competitive inhibitor of bacterial adherence; in sufficient concentration in urine D-mannose causes saturation of FimH adhesins and prevents the bacteria from binding to urothelial receptors. As well as *in vitro*, reduction of bacteriuria levels has also been confirmed in *in vivo* animal UTI models [1]. A similar anti-adhesive effect mechanism has been suggested for Tamm–Horsfall protein. The mannose-containing side chains of the protein bind bacteria and facilitate their elimination [2]. It is important to note that the anti-adhesive effect of mannose depends on the configuration of the molecule. Only D-isomer and α-anomer (α-D-mannose) can bind and block the FimH adhesin. Other carbohydrates have little or no anti-adhesive effect [3].

D-mannose powder has been available for some time for the treatment of UTIs in horses, cats and dogs. Its efficiency has not been validated in larger studies but it has been shown that *in vitro* D-mannose applied locally reduces the adherence of *Escherichia coli*, *Pseudomonas aeruginosa* and *Streptococcus zooepidemicus* (important causes of sterility in mares) to endometrial epithelial cells in mares [4]. D-mannose is also widely available and used for UTI prevention in humans as a food supplement, but clinical studies on the topic are lacking; therefore, in 2012, after obtaining institutional ethics board approval, we conducted a clinical trial that included 308 women >18 years of age with acute UTI and a history of recurrent UTIs [5]. We did not include patients who had urinary tract anomalies, interstitial cystitis or diabetes, and those who were pregnant or taking hormone therapy/contraception. The primary outcome measure of the trial was the reduction in microbiologically proven UTI.

After initial antibiotic treatment of the acute UTI (ciprofloxacin 500 mg twice daily for 1 week), patients were randomly allocated to three equal groups. The first group received prophylaxis with 2 g of D-mannose powder daily for 6 months, the second received prophylaxis with 50 mg of nitrofurantoin once a day, and the third did not receive prophylaxis. During the 6-month study period 98 of our patients (32%) had a recurrent UTI. The rate of recurrent UTI was significantly higher in the group that did not receive prophylaxis (60%) compared with the groups receiving D-mannose (15%) and nitrofurantoin (20%) which did not differ significantly. The risk of recurrent UTI episodes was significantly higher in the no-prophylaxis group compared with the groups that received active prophylaxis (relative risk 0.24 and 0.34). Also, we found that patients in the D-mannose

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group had a significantly lower risk of side effects compared with patients in the nitrofurantoin group, although nitrofurantoin was generally well tolerated. In patients who were taking D-mannose, episodes of diarrhoea were the only side effect and were noted in 8% of patients, but they did not require discontinuation of the prophylaxis. Patient compliance (assessed by recording the intake of prophylaxis on a self-report sheet) was very high and there was no difference between patients taking nitrofurantoin or D-mannose.

The results of this study suggest that D-mannose can be an effective prophylactic agent in a selected population; however, more studies will certainly be needed to confirm the results of our study, especially because of the experience with cranberry products in UTI prevention. Similarly to D-mannose, it has been shown in multiple *in vitro* studies that cranberry inhibits bacterial adherence to urothelial cells but in clinical practice different results have been reported. The usefulness of cranberry products in preventing recurrent UTIs has not been clearly established, although it is still widely used and prescribed to patients. The latest Cochrane Database review concluded that cranberry products cannot currently be recommended for the prevention of recurrent UTIs [6], although there are many good-quality studies that clearly showed its efficacy in selected patients. A possible cause of such a finding and contrasting results among clinical studies is that in many of them various cranberry products (powder, juice, capsules) without clearly defined potency, dosing and active ingredient contents have been used, which is a known problem with natural food supplements. To avoid such issues with D-mannose, pharmacokinetic studies to determine the exact dosage and optimum regimen for D-mannose should be undertaken in further research. We believe that D-mannose may be a useful agent for the prevention of recurrent UTIs but further clinical trials will be necessary.

Conflict of Interest

None declared.

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