Is it possible to improve elderly male bladder function by having them drink more water? A randomized trial of effects of increased fluid intake/urine output on male lower urinary tract function.

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IS IT POSSIBLE TO IMPROVE ELDERLY MALE BLADDER FUNCTION BY HAVING THEM DRINK MORE WATER? A RANDOMIZED TRIAL OF EFFECTS OF INCREASED FLUID INTAKE/URINE OUTPUT ON MALE LOWER URINARY TRACT FUNCTION

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ABSTRACT

Objectives. Several animal studies have shown that bladder performance improves as a result of diuresis. Whether increased urine output also has beneficial effects on elderly male bladder function and lower urinary tract symptoms is unknown.

Methods. We performed a randomized placebo-controlled trial of 141 men, 55 to 75 years of age, with moderate lower urinary tract symptoms. The experimental group drank 1.5 L of extra water daily. The control group consumed one tablespoon of placebo syrup daily. After 6 months, we evaluated bladder contractility, voided volumes, and the severity of lower urinary tract symptoms. The actual increase in water consumption was measured using the deuterium urine dilution method.

Results. Water consumption in the intervention group increased by 359 mL (95% confidence interval [CI] 171 to 548) per 24 hours compared with the control group. At 6 months, no statistically significant effect was found in the maximal flow rate (0.9 mL/s, 95% CI −0.4 to 2.2) compared with placebo. A statistically significant effect was found for bladder pressure (20 cm H_2O, 95% CI 6 to 34) and bladder wall stress (1.9 N/cm^2, 95% CI 0.3 to 3.5). In addition, it showed that the experimental group had greater maximal (44 mL, 95% CI −1 to 90) and average (26 mL, 95% CI 1 to 51) voided volumes per urination. The subjective effect parameters improved in both groups, but no statistically significant differences were found between the two groups.

Conclusions. It seems possible to improve some aspects of male bladder function by drinking more water. However, the effects are too small to be clinically relevant. UROLOGY **68:** 1031–1036, 2006. © 2006 Elsevier Inc.

The aim of our research was to test a possible preventive intervention for lower urinary tract symptoms (LUTS) in elderly men. LUTS are present in approximately 20% to 30% of the elderly male population.[1] Because of the high prevalence and the associated costs, the prevention of these symptoms is of great importance from a health policy perspective.[2]

Several animal studies have shown that bladder performance can be improved by increasing the urine output.[3,4] It is assumed that this is an adaptive response to an increased physiologic load. This response is essentially different from the pathologic adaptation observed in the case of bladder outlet obstruction.[5] In the latter, after an initial adaptation, a marked increase in bladder mass and a decrease in both compliance (flexibility) and contractility occur.[5] In the case of increased diuresis, the animal bladder mass is also increased, but the compliance and contractility improve.[3,4]

The animal study findings made us wonder

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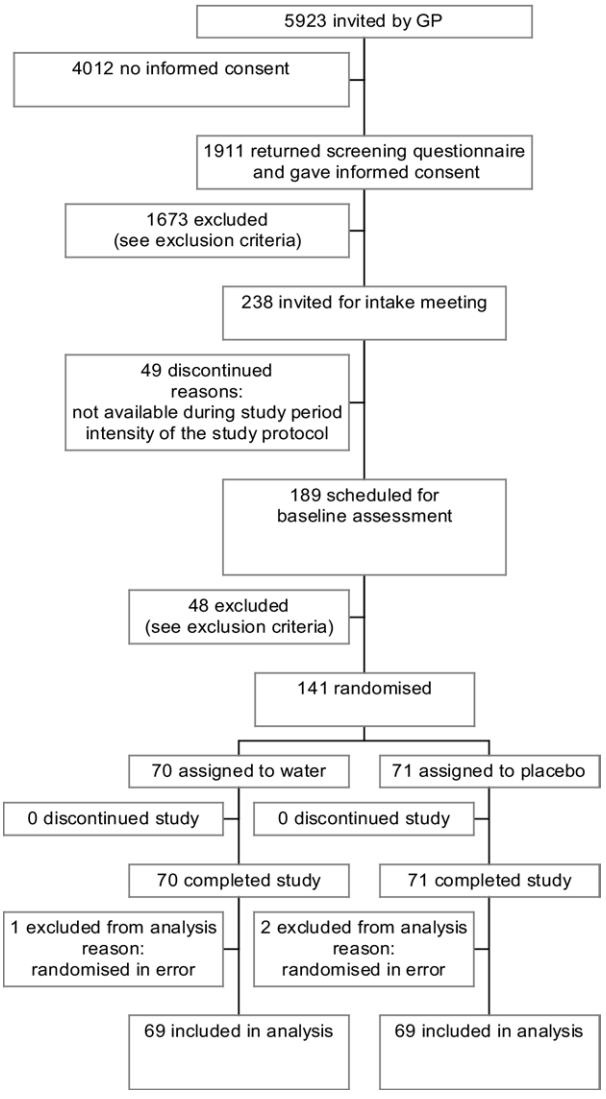

FIGURE 1. *Trial profile.*

whether it would be possible to improve the function of the human urinary tract by increasing the urine output.[6] In humans, an increased urine output can be achieved by increasing the fluid intake. In a previously published uncontrolled study, we observed a gradual improvement in the maximal urinary flow rate and maximal and average voided volumes after 2 months of increased fluid intake.[7] These preliminary findings seemed to support our hypothesis.

The next step was to study the long-term effects in a controlled study. We report on a randomized placebo controlled trial in which we studied the effects of increased fluid intake on elderly male lower urinary tract function and LUTS.

MATERIAL AND METHODS

Participants

The study population was recruited using 21 general practices. Figure 1 shows the trial profile of this study. The general practitioners invited their total male population between 55 and 75 years of age to participate. A screening questionnaire, containing the International Prostate Symptom Score (IPSS; range 0 to 35),[8] questions on comorbidity, and a 24-hour drink diary, together with the informed consent documents, were enclosed with the doctor's invitation. A total of 1911 men gave informed consent and were screened for moderate LUTS (IPSS 8 to 19). The main exclusion criteria were the presence of mild (IPSS 0 to 7) or severe (IPSS 20 to 35) LUTS and a self-reported fluid intake greater than 2 L/day. The other exclusion criteria were the presence of diabetes, Parkinson's disease, or renal disease; previous surgery of the lower urinary tract; a history of prostate or bladder carcinoma; and the use of diuretics, medication for LUTS, or tricyclic antidepressive agents. We excluded 1673 men on the basis of these criteria. The remaining 238 men were invited for an intake visit and a baseline assessment. At this point, participants were excluded if no baseline assessment was possible (eg, inability to urinate in the presence of the assessor), if prostate cancer was diagnosed (prostate-specific antigen level greater than 4.0 μg/L followed by biopsy to confirm the presence of carcinoma), or if they had a serum sodium level less than 130 mmol/L.

Randomization and Interventions

A person, who was otherwise not involved in the execution of the study and had no access to the baseline data, generated the random allocation sequence with a computerized random-number generator and randomly assigned the participants to two groups. A person, who was not involved in the effect measurements, instructed the men in the intervention group to drink 1.5 L of water daily, in addition to their normally consumed beverages, for a 6-month period. They were advised to divide this amount into three portions of 0.5 L spread throughout the day. To improve the adherence to the intervention, they were supplied with 0.5-L glasses. The control group received a placebo intervention in the form of placebo syrup (one tablespoon [8 mL]) each day during dinner, also for a 6-month period.

The participants were not given any information on the specific goal of the interventions to accomplish blinding of the nature of the interventions and the hypothesis of this study. A detailed description of the methodologic and ethical aspects of this trial has been previously published.[9] The ethical review committee of the University Hospital Maastricht/University of Maastricht approved the research protocol and the informed consent procedure.

All parameters were recorded at baseline and at 6 months (immediately after termination of the intervention period).

Objective Effect Parameters

The objective measurements were conducted at the Maastricht University Hospital, Department of Urology. Seven participants were scheduled for each session, which lasted approximately 4 to 5 hours. We asked them to drink a lot of water during each session so that they would produce enough urine to void four times.

The maximal urinary flow rate (Qmax) was assessed two times by measuring the voided volume per unit of time with a Dantec flow meter.[10] We calculated the mean of the measurements if both recorded voidings were valid (ie, voided volume greater than 150 mL); otherwise only the valid measurement was included in the final analysis. Isovolumetric bladder pressure was assessed two times using the condom catheter method.[11–13] In this procedure, the patient voids through a modified incontinence condom that is connected by way of a measurement unit to three tubes. Next, voiding is interrupted by closing the tubes, and the pressure inside the condom is measured. This pressure represents the isovolumetric bladder

pressure. The maximal value attained in the two measurements was included in the analysis. Bladder wall thickness was assessed by ultrasonography by measuring the thickness of the anterior bladder wall.[14,15] The measurements were performed two times using a Hitachi EUB 6000 with a 3.5-MHz probe. The thickness of the anterior bladder wall was measured at three points with the transducer suprapubically placed in the sagittal plane with each subject in supine position. We then calculated the mean of these three observations for each measurement and subsequently the mean of the two mean values. The measured thickness was not corrected for bladder volume.[15]

In addition, we measured the volume of the bladder before the measurement of the isovolumetric bladder pressure using the same ultrasound equipment. By combining the isovolumetric bladder pressure, bladder volume, and bladder wall thickness, the maximally generated bladder wall stress was calculated according to the method described by Bross *et al.*[16] The postvoid residual urine volume was also assessed by ultrasound after each measurement of the Qmax. A mean of the two measurements was calculated. In addition to these measurements performed in the hospital, we calculated the maximal and average voided volume per urination from a 24-hour frequency volume chart.[17]

Subjective Effect Parameters

The global perceived benefit of the intervention was measured with the question: "How did your urinary condition change since treatment initiation?" (7-point scale: 0 = much worse to 6 = much better). The scores were recoded into a 3-point scale indicating worsening (score 0 to 2), no change (score 3), and improvement (score 4 to 6) of urinary tract function. Patients answered the IPSS questionnaire[8] and quality-of-life question (range 0 to 6) to assess symptom severity and bother.

Assessments of Covariates

We classified the subjects into obstructed and nonobstructed patients by combining the Qmax with the isovolumetric bladder pressure using the following strategy: Qmax less than 4.5 mL/s indicated obstructed; Qmax greater than 13.8 mL/s indicated nonobstructed; and Qmax 4.5 to 13.8 mL/s indicated obstructed if the measured bladder pressure was greater than $36.4 + 5.8 \times$ Qmax. This method has been described by Pel *et al.*[18] Obstruction was used as a stratification factor in the randomization procedure. In addition, we measured the prostate size using a 6.5-MHz rectal probe.

Assessment of Adherence

We measured the adherence to the experimental intervention with deuterium-labelled water. The deuterium method is considered the reference standard for measuring water turnover in humans.[19,20] After ingestion, deuterium mixes with the total body water and is eliminated at a rate dependent on the rate of water turnover. Therefore, by plotting the deuterium concentration in the urine against time, we were able to determine the total water turnover per 24 hours. The experimental and control groups followed the deuterium protocol for 2 weeks before the baseline assessment in the hospital and during the final 2 weeks of the intervention period.

Sample Size

With an assumed standard deviation (SD) of 5.2 (derived from el Din *et al.*[21]), we needed 68 patients per group to detect a clinically worthwhile effect of 2.5 mL/s on Qmax (0.9 power, alpha = 0.05, two-sided). With this sample size, we were able to detect a difference of 1.5 points on the IPSS (assumed SD 3.2[21]). A total of 141 participants were enrolled in the study (Fig. 1). Three subjects were ineligible because they had a baseline IPSS score greater than the maximum of 19 points (score of 20, 21, and 22). They were, therefore, excluded from the final statistical analysis.

Statistical Analysis

For the estimation of the treatment effect, we performed multiple linear regression analyses (analysis of covariance) in which the follow-up measurement was used as the outcome variable, the intervention type as the predictive variable, and the baseline score of that outcome variable, prostate size, and age as covariates.[22,23] The randomization code was revealed to the researchers after the first main statistical analyses were performed. We used an intent-to-treat analysis and the Statistical Package for Social Sciences (SPSS, Chicago, Ill). As a per protocol analysis, the analysis was subsequently done without the subjects in the experimental intervention group who had not increased their water turnover greater than the median (intervention group) level. In addition, we studied the linear relationship between the effect measures and actual increase in water turnover (linear regression analysis). We determined the 95% confidence intervals, and a two-tailed P value less than 0.05 was considered statistically significant.

RESULTS

Objective Effects

The effects of the experimental intervention on the bladder are shown in Table I. At 6 months, no statistically significant effect of increased water intake was found on Qmax compared with placebo, but the intervention group scored better on two other measures of bladder contractility—bladder pressure and bladder wall stress. No statistically significant effect was found on bladder wall thickness or postvoid residual urine volume.

In terms of the storage function of the bladder, it showed that the experimental group had greater maximal, as well as average, voided volumes per urination at 6 months; the effect on the average voided volume was statistically significant.

Subjective Effects

At 6 months, 7 men (10%) in the experimental group reported a worsening and 42 men (61%) reported an improvement of their urinary function compared with 5 (7%) and 34 (49%) in the control group (chi-square $P = 0.2$; data not shown in Table I). Both groups had a lower total IPSS and IPSS quality of life score at 6 months. The mean irritative score decreased significantly more in the placebo group and the obstructive symptoms changed insignificantly in favor of the experimental group.

Treatment Adherence

The 24-hour water turnover in the experimental group increased by 1030 ± 586 mL from 3034 ± 631 mL at baseline (data not shown). The water turnover in the control group was 2950 ± 498 mL at baseline and was 672 ± 443 mL greater at 6

TABLE I. *Changes in effect parameters between increased water intake and control*

Variable	Control (n = 69)	Water (n = 69)	Effect of Water* (95% CI)	*P* Value
Objective effect parameters				
Maximal urine flow rate (mL/s)				
Baseline	17.5 (6.8)	15.8 (5.6)		
6 mo	16.3 (6.5)	15.8 (5.4)	0.9 (−0.4 to 2.2)	0.2
Isovolumetric bladder pressure (cm H_2O)				
Baseline	124 (45)	128 (53)		
6 mo	110 (40)	131 (58)	20 (6–34)	0.007
Bladder wall thickness (mm)				
Baseline	1.9 (0.3)	1.9 (0.3)		
6 mo	2.1 (0.3)	2.1 (0.3)	0.03 (−0.1 to 0.1)	0.6
Bladder wall stress (N/cm^2)				
Baseline	13.8 (5.5)	13.4 (5.8)		
6 mo	11.5 (4.7)	12.9 (5.7)	1.9 (0.3–3.5)	0.02
Postvoid residual urine volume (mL)				
Baseline	168 (113)	134 (107)		
6 mo	169 (123)	143 (117)	−5 (−39 to 29)	0.8
Maximal voided volume per urination (mL)				
Baseline	351 (117)	345 (132)		
6 mo	337 (135)	381 (138)	44 (−1 to 90)	0.05
Average voided volume per urination (mL)				
Baseline	218 (78)	205 (75)		
6 mo	206 (87)	226 (65)	26 (1–51)	0.04
Subjective effect parameters				
Symptoms (IPSS; 0–35)				
Baseline	13.4 (3.1)	12.2 (3.3)		
6 mo	11.2 (4.3)	11.1 (4.2)	0.5 (−0.9 to 2.0)	0.5
Irritative symptoms (IPSS items 2, 4, 7; 0–15)				
Baseline	5.7 (2.8)	6.0 (2.6)		
6 mo	4.4 (2.5)	5.8 (2.5)	1.3 (0.6–2.1)	<0.001
Obstructive symptoms (IPSS items 1, 3, 5, 6; 0–20)				
Baseline	7.7 (2.8)	6.2 (2.8)		
6 mo	6.8 (3.4)	5.2 (2.6)	−0.7 (−1.7 to 0.2)	0.139
IPSS Quality of Life (0–6)				
Baseline	2.9 (1.0)	2.6 (1.0)		
6 mo	2.5 (1.2)	2.3 (0.9)	0.1 (−0.2 to 0.4)	0.6

KEY: CI = confidence interval; IPSS = International Prostate Symptom Score (lower scores indicate more favorable score).
Data presented as mean, with SD in parentheses.
** Estimated effect (effect size) was determined with regression analysis in which we adjusted for differences in baseline score, prostate size, and age.*

months. The effect of the experimental intervention compared with the placebo was 359 mL (95% confidence interval 171 to 548).

Per Protocol Analysis

Excluding the participants from the experimental group who had a water turnover of less than the median score of 955 mL did not increase the effects (effect of water on Qmax, 0.7 ± 0.9 mL/s; on bladder pressure, 15 ± 9 cm H_2O; on IPSS, 0.8 ± 0.9). In addition, it showed that changes in the Qmax, isovolumetric bladder pressure, and IPSS could not be predicted by changes in water turnover (coefficients for 1-L increase in water turnover: Qmax, 1.0 ± 0.7 mL/s, bladder pressure, −1.4 ± 7.6 cm H_2O; IPSS −0.09 ± 0.7).

Analysis of Effect Modification of Age and Obstruction

The interaction terms for obstruction and age were not statistically significant for all outcome measures, indicating that the effect of the intervention was not significantly different for the obstructed versus nonobstructed participants or for the older versus younger participants (data not shown). In addition, no clinically relevant differences between the age and obstruction subgroups were observed in the stratified analyses for the effects on Qmax, bladder pressure, and IPSS (data not shown).

COMMENT

The results of animal studies formed the basis of our hypothesis that the human bladder could fa-

vorably adapt to increased loading. There was no reason to assume that animal-like effects would not be possible in humans. In addition to these animal studies, the results of an uncontrolled study of 44 elderly men showed positive effects and therefore seemed to confirm our ideas.[7] In this trial, 6 months after we gave the advice to increase the daily fluid intake by 1.5 L, we found some statistically significant, but modest, effects on bladder function. No important effects were found on the subjective effect parameters.

It has been shown that many urologists (69%) use lifestyle interventions in the treatment of LUTS.[24] Such advice may include fluid restriction, caffeine or alcohol avoidance, rescheduling medication such as diuretics, retraining of "bad" voiding habits, and many other instructions.[24] However, at present, these instructions seem to be based on clinical experience or findings from etiologic studies, because we found no randomized trials in which the effects of self-management as an intervention for men with LUTS were investigated. Only one study was found that made an attempt to construct a self-management program.[25] Because LUTS is more of a functional, than an anatomic, disorder, we believe that self-management interventions should be investigated more often.

An important limitation of our study was the relatively poor contrast between the two study groups. This may partly explain the relatively small effects. In the animal studies, using diuretics, a 200% to 300% increase in urine output was achieved.[3,4] In our study, we accomplished a contrast of approximately 10% at the end of the study. This contrast might have been larger if the Dutch summer of 2003 had not been the second warmest summer in the past 100 years. The hot summer increased the water turnover in the control group, reducing the contrast between the two groups.

Despite the poor contrast, we observed some statistically significant effects. It seems, therefore, that the bladder responded; although the observed effects were not clinically relevant. Future studies on the adaptive capability of the bladder must put much effort in achieving a more profound contrast. Another approach that might improve the adaptability of the bladder is to improve the bladder blood flow. The reduced vascularization and innervation of the elderly bladder[26,27] probably impairs the adaptive capacity. Some evidence has suggested that alpha-blockers[28] and aspirin[29] improve bladder blood flow. These agents might be used in combination with increased urine output to improve the adaptive capability of the bladder.

CONCLUSIONS

It seems possible to improve elderly male bladder function by increased physiologic loading, but the method we used to increase the urine output (ie, to drink 1.5 L of water) produced effects that were too small. Future research should focus on finding ways to achieve a large increase in urine output without compromising the feasibility of the intervention.

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