Determinants of Nocturia: the Krimpen Study

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Abbreviations and Acronyms

24HVV = 24-hour voided volume

COPD = chronic obstructive pulmonary disease

FVC = frequency-volume chart

GLMM = generalized linear mixed effect model

GP = general practitioner

LUTS = lower urinary tract symptoms

MVV = maximum voided volume

NP = nocturnal polyuria

NUP = nocturnal urine production

NUP90 = NP defined as urine production greater than 90 ml per hour between 1:00 a.m. and 6:00 a.m.

NUV = nocturnal voided volume

NUV33 = NP defined as nocturnal urine volume greater than 33% of 24HVV

NVF = nocturnal voiding frequency

PVR50 = post-void residual greater than 50 ml

Qmax = maximum flow rate

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Purpose: Many conditions and characteristics are cross-sectionally associated with nocturia. However, to our knowledge longitudinal associations of frequency-volume chart based nocturia have not yet been studied. We identify (modifiable) determinants of nocturia in older men in a longitudinal setting.

Materials and Methods: A longitudinal, community based study was conducted among 1,688 men age 50 to 78 years in Krimpen aan den IJssel, The Netherlands with planned followup rounds at 2, 4 and 6 years. Men without a history of radical prostatectomy, transurethral surgery, or bladder or prostate cancer were included in the study. Data were obtained using frequency-volume charts, from which the nocturnal voiding frequency, maximum voided volume and (nocturnal) urine production were determined. Nocturia was defined as a nocturnal voiding frequency of 2 or more episodes. Polyuria was defined as greater than 2,800 ml voided per 24 hours. For nocturnal polyuria we used the 2 definitions of 1) greater than 33% of 24-hour voided volume and 2) nocturnal urine production of greater than 90 ml per hour. Conditions and characteristics were determined via medical examinations and questionnaires. A generalized linear mixed effect model was used to determine factors longitudinally associated with nocturia.

Results: Age (50 to 55 years vs greater than 60 years), maximum voided volume (greater than 300 ml vs less than 300 ml), 24-hour polyuria, nocturnal polyuria (both definitions) and lower urinary tract symptoms were all longitudinally associated with an increased prevalence of nocturia in older men.

Conclusions: A smaller maximum voided volume, lower urinary tract symptoms, 24-hour polyuria and nocturnal polyuria are significant and potentially modifiable determinants of nocturia. The finding that both definitions for nocturnal polyuria are independent significant determinants may indicate a 2-step etiologic process for nocturnal polyuria.

Key Words: nocturia, lower urinary tract symptoms, epidemiology, polyuria, prostatic hyperplasia

NOCTURIA is a prevalent symptom that may cause considerable bother in the case of 2 or more episodes per night.[1–5] Cross-sectional associations have been shown between nocturia and conditions such as nocturnal polyuria, obesity, benign prostatic enlargement and depression.[5–8] However, longitudinally, analyses of the determinants of nocturia are limited to the TAMUS (Tampere Aging Male Urological Study).[1] Although the

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study was well performed, the value of the information from the TAMUS remains uncertain. That study is based on the DAN-PSS-1 (Danish Prostatic Symptom Score) questionnaire,[2] and because of its response categories, it does not allow the determination of exact nocturnal voiding frequency.[3,4] Furthermore, voided volumes and urine production estimates are not taken into account, and the followup period is relatively short.

Frequency-volume charts may represent a more objective method of assessing nocturia because no recall bias is involved.[6] The association between questionnaire data and FVCs is only modest,[7] and no longitudinal data are available on FVC assessed nocturia. Such analyses are needed to identify modifiable determinants of nocturia. Therefore, in this study we identify longitudinal determinants of nocturia.

MATERIALS AND METHODS

The Krimpen study is a longitudinal analysis of urogenital tract dysfunction and its impact on general health status. The design of this study has been described extensively elsewhere.[9] All men age 50 to 78 years in a Dutch municipality (reference date June 1995, sample size 3,924) were investigated. Exclusion criteria were prostatectomy, prostate or bladder cancer, neurogenic bladder disease or negative advice from their GP based on poor health.

At baseline the participants completed a 113-item questionnaire which addressed chronic diseases, smoking, alcohol intake and the I-PSS (International Prostate Symptom Score). Subsequently participants visited the local GP health center for a medical examination. Appointments were made for urological measurements at the Erasmus Medical Center Rotterdam urological outpatient department. Participants were also instructed to complete a FVC.

Followup

Followup rounds were planned after 2, 4 and 6 years.[10] All baseline measurements were repeated under the same conditions at the respective followup rounds. If participants had not died or moved away and no exclusion criteria were met, the GPs were asked to send a reinvitation letter for the followup rounds. At the third followup round all nonresponders of the previous rounds were re-invited.

NUP and Voided Volumes Determined Via FVCs

On their FVC the participants reported each micturition in 1-hour time units (eg "n" micturitions between 12:00 and 13:00) for 3 days. In addition, they recorded the volume of each void on the third day. Recording of each day started at midnight (00:00) and ended at midnight (24:00), ensuring the first morning void was always included.[8] Nighttimes, as defined by the ICS (International Continence Society) were noted[4] and fluid intake was not recorded, which complies with the ICS definition of a FVC.[11]

We computed hourly urine production according to the method of van Mastrigt and Eijskoot, in which urine production was assumed to be constant between voids, and hourly urine production was estimated as the volume of each micturition divided by the number of hours that passed since the previous micturition.[12] Nocturnal urine production was estimated as the mean hourly urine production from 1:00 a.m. to 6:00 a.m., when more than 90% of the men were asleep.[8] Four consecutive hours of nighttime was the minimum for inclusion.

Nocturnal voided volume was determined by using participant reported nighttimes, and the voided volumes between bedtime and hour of rising plus the first morning void were summed.

Several variables were also determined via FVC, including maximum voided volume (defined as the largest voided volume during 24 hours), 24HVV and nocturnal voiding frequency (defined as the number of voids between declared hours of nighttime). NVF does not include voids before going to sleep and at the time of rising. Nocturia was defined as NVF 1 or more by the ICS. However, because this is prevalent and because NVF less than 2 does not seem to cause bother, we defined nocturia as NVF 2 or greater to study the determinants of nocturia that might be clinically relevant.[5,7]

Polyuria and Nocturnal Polyuria

For polyuria we used the ICS definition of a 24HVV greater than 2,800 ml.[11] Although usually weight corrected, we used this fixed definition for practical purposes. We applied 2 definitions of nocturnal polyuria. We used the definition proposed by the ICS in which NP is defined as NUV greater than 33% of the 24HVV (NUV33) in people older than 65 years.[4] Although the median participant age at baseline was 61.6 years, we used this definition for all our subjects for practicality. For comparison purposes we also used the definition of NP as nocturnal urine production greater than 90 ml per hour (NUP90). This definition was chosen because it was previously determined to be the strongest predictor of nocturia.[8]

Lower Urinary Tract Symptoms

The 7-item I-PSS questionnaire was used to determine the severity of LUTS. However, in this analysis we did not use question 7 on nocturia to prevent outcome association.[13,14] For clarity we renamed it I-PSS-6.

Statistical Analyses

We analyzed the data of all men who completed the FVC including reported nighttimes. Data on these participants were collected during the 4 rounds. To examine generalizability we compared baseline characteristics of men included in the study and those excluded from analysis because they failed to declare nighttimes. For dichotomous variables chi-square tests were used, and for age and LUTS the Mann-Whitney U test was used.

A generalized linear mixed effect model was used to examine the determinants of nocturia. Essentially a GLMM is similar to multiple regression analysis but allows correlation between repeated measurements and is able to adjust for unequal followup times, missing data and fluctuating variables (eg hypertension, nocturia).[1,14,15]