

Investigation of biochemical factors related to non-bothersome nocturnal urination

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ABSTRACT

We investigated the factors related to nocturnal urination that was not considered bothersome by comparing various parameters between subjects who felt nocturnal urination as bothersome and those who did not. A total of 94 persons (50 males and 44 females) were enrolled. They urinated \geq once per night. Each subject's perception of nocturnal urination was examined, and the subjects were divided into a bothersome group and a non-bothersome group. Blood biochemical data and urinary condition were compared between the two groups and various subgroups. There were 60 subjects (56 ± 17 years old) in the non-bothersome group, and 34 subjects (57 ± 17 years old) in the bothersome group. The serum melatonin level was significantly lower and the total score of the International Prostatic Symptom Score questionnaire (IPSS) and the quality of life (QOL) score were significantly higher in the bothersome group than in the non-bothersome group. Among 50 subjects with nocturnal urination \geq twice per night, the serum melatonin level was also significantly lower and the QOL score was significantly higher in the bothersome group than in the non-bothersome group. In conclusion, nocturnal urination might be not considered bothersome when subjects maintain sufficient levels of melatonin.

Nocturnal urinary frequency, a common symptom in the elderly, is one of the most bothersome urologic symptoms (3). Nocturia is defined as the complaint that the individual has to wake once or more times during the night to void (1), and may result in sleep disturbance that causes daytime fatigue as well as worsening the quality of life (QOL) (2, 3). However, patients are not certain why they wake up and go to the toilet in the night: it is strong urgency for some and it is insomnia for others (12). Multiple

factors may contribute to the occurrence of nocturia, including pathological conditions such as cardiovascular disease, diabetes mellitus, lower urinary tract obstruction, anxiety disorders or primary sleep disorders as well as various other behavioral and environmental factors (8, 18). Recently published guidelines have attributed the occurrence of nocturia to nocturnal polyuria and/or diminished nocturnal bladder capacity (17). This classification has been widely accepted and used to determine various treatments. However, some elderly persons do not consider nocturnal urination to be bothersome even if they have a number of episodes, while other persons feel bothered even if they wake up once per night. Accordingly, a therapy to target the perception of nocturnal urination as non-bothersome seems worthwhile to pursue, even though the actual decrease in the number of urinations may be small.

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In this study, we therefore investigated the factors related to nocturnal urination that was not considered bothersome by comparing various parameters between subjects who felt nocturnal urination as bothersome and those who did not.

SUBJECTS AND METHODS

The subjects were selected from among outpatients who consulted the Department of Urology at our University Hospital or an affiliated hospital between January 2005 and February 2007. Patients who met the following criteria were enrolled: 1) their lower urinary tract symptoms—except for nocturnal urination—were controlled by medication (adrenergic alpha-1 receptor antagonists, anti-muscarinic agents, and/or herbal medicines) over a period of 2 months; 2) they had urination \geq once per night; 3) they did not have neurological or psychological abnormalities, hepatic dysfunction, renal dysfunction, diabetes mellitus, or cardiovascular disease; and 4) they were not taking either tranquilizers, hypnotics, or melatonin. Patients with bacterial cystitis, bacterial prostatitis, urinary tract cancer, hematuria, or proteinuria were excluded. A total of 94 persons (50 males and 44 females aged 26–93 years) consented to this study and were enrolled. All 50 male patients had benign prostatic enlargement with or without an overactive bladder, while the 44 female patients had urethral syndrome and/or overactive bladder. Their residual urine volume was < 20 mL on abdominal ultrasonography.

We examined the average number of daytime urinations over one month, the average number of nocturnal urinations during the sleeping period, the International Prostatic Symptom Score questionnaire (IPSS), the QOL score (happy: 0, satisfied: 1, almost satisfied: 2, not satisfied/not dissatisfied: 3, slightly dissatisfied: 4, dissatisfied: 5, unhappy: 6), and the perception of nocturnal urination (not bothersome, slightly bothersome, bothersome, or very bothersome). Subjects who stated that it was not or slightly bothersome were assigned to the non-bothersome group. When subjects stated that it was bothersome or very bothersome, they were assigned to the bothersome group. These groups were also stratified into subgroups by the frequency of nocturnal urination.

Blood samples were taken from all subjects at 10–12 a.m. Then the complete blood count (white blood cells: WBC, red blood cells: RBC, hemoglobin: Hb, hematocrit: Ht, platelets: Plt) was measured, and biochemistry tests (serum total protein:

TP, albumin: ALB, aspartate aminotransferase: AST, alanine aminotransferase: ALT, lactate dehydrogenase: LDH, cholinesterase: ChE, gamma-glutamyl transpeptidase: γ -GT, total bilirubin: T-Bil, blood urea nitrogen: BUN, creatinine, melatonin, and plasma arginine-vasopressin: AV, adrenalin, noradrenalin, dopamine, serotonin, human atrial natriuretic peptide: HANP, brain natriuretic peptide: BNP) were performed. The blood viscosity (14) and the plasma osmotic pressure were also measured. These data were compared between the two groups and the subgroups.

Results are reported as the mean \pm standard deviation (SD). Student's unpaired *t*-test was used for statistical analysis, and $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Among the 94 subjects with urination \geq once per night, 60 subjects (32 males and 28 females aged 56 ± 16 years) were in the non-bothersome group, and 34 subjects (18 males and 16 females aged 57 ± 17 years) were in the bothersome group. However, the rate of subjects in the non-bothersome group gradually decreased with an increase in frequency of nocturnal urination, and the number of subjects in the bothersome group became larger than that in the non-bothersome group when the subjects were limited to those with urination ≥ 4 times per night (Table 1).

Among the 94 subjects with urination \geq once per night, the serum melatonin level of the bothersome group was significantly lower ($p = 0.047$) than that of the non-bothersome group (Table 2). The urinary frequency at nighttime, the total score of the IPSS, and the QOL score of the bothersome group were significantly higher ($p = 0.004$, $p = 0.049$ and $p < 0.001$, respectively) than those of the non-bothersome group (Table 3). There were no significant differences in other parameters between the two groups.

Among the 50 subjects with urination \geq twice per night, the serum melatonin level of the bothersome group (15 males and 9 females aged 65 ± 13 years) was significantly lower ($p = 0.023$) than that of the non-bothersome group (15 males and 11 females aged 62 ± 16 years) (Table 4). The QOL score of the bothersome group was significantly higher ($p < 0.001$) than that of the non-bothersome group (Table 5). There were no significant differences in other parameters between these two subgroups.

Table 1 Relationship between frequency of nocturnal urination and urinary bothersome

Frequency of nocturnal urination	Sex	non-bothersome	bothersome	Total
≥ once	Male	32	18	50
	Female	28	16	44
	Sub total	60 (64%)	34 (36%)	94 (100%)
≥ twice	Male	15	15	30
	Female	11	9	20
	Sub total	26 (52%)	24 (48%)	50 (100%)
≥ 3 times	Male	9	10	19
	Female	5	2	7
	Sub total	14 (54%)	12 (46%)	26 (100%)
≥ 4 times	Male	5	7	12
	Female	2	1	3
	Sub total	7 (47%)	8 (53%)	15 (100%)

Table 2 Blood examination in subjects with non-bothersome (n = 60) or bothersome (n = 34) nocturnal urination ≥ once per night

Nocturnal urination ≥ once per night	Age	TP	ALB	AST	ALT	LDH
		g/dL	g/dL	IU/L	IU/L	IU/L
non-bothersome	55.6 ± 15.8	7.4 ± 0.5	4.4 ± 0.3	23 ± 9	23 ± 14	198 ± 41
bothersome	57.1 ± 17.4	7.4 ± 0.5	4.3 ± 0.3	23 ± 9	24 ± 17	192 ± 46
	CHE	T-Bil	BUN	Cre	Melatonin	AV
	IU/L	mg/dL	mg/dL	mg/dL	pg/mL	pg/mL
non-bothersome	349 ± 66	0.4 ± 0.2	14.0 ± 3.9	0.8 ± 0.2	4.1 ± 3.8	1.6 ± 0.8
bothersome	342 ± 73	0.5 ± 0.5	14.7 ± 4.8	0.8 ± 0.2	3.0 ± 1.0]*	1.6 ± 0.7
	Adrenalin	Noradrenalin	Dopamine	Serotonin	Blood viscosity	HANP
	pg/mL	pg/mL	pg/mL	µg/mL	mP • s	pg/mL
non-bothersome	38 ± 21	483 ± 216	14.1 ± 7.5	0.02 ± 0.02	5.27 ± 0.75	17 ± 11
bothersome	33 ± 16	461 ± 205	13.5 ± 8.7	0.02 ± 0.01	5.17 ± 0.61	19 ± 19
	BNP	WBC	RBC	Hb	Ht	Plt
	pg/mL	/µL	x10000/µL	g/dL	%	x10000/µL
non-bothersome	20 ± 28	6448 ± 1797	448 ± 72	14.2 ± 2.2	43.8 ± 5.7	24.7 ± 6.7
bothersome	30 ± 48	6232 ± 1565	452 ± 43	14.2 ± 1.5	43.1 ± 6.7	22.8 ± 5.7

mean ± SD, *: p < 0.05

Table 3 Urinary condition in subjects with non-bothersome (n = 60) or bothersome (n = 34) nocturnal urination ≥ once per night

Nocturnal urination ≥ once per night	Urinary frequency at daytime	Urinary frequency at nighttime	IPSS							QOL score	
			Incomplete emptying	Frequency	Intermittency	Urgency	Weak stream	Hesitancy	Nocturnal urination		IPSS-total
non-bothersome	6.9 ± 2.7	1.8 ± 1.1]**	0.6 ± 1.2	1.3 ± 1.3	0.7 ± 1.5	0.7 ± 1.1	1.0 ± 1.6	0.6 ± 1.4	1.8 ± 1.0]**	6.7 ± 5.9]*	2.3 ± 1.8]***
bothersome	7.6 ± 3.9	2.5 ± 1.5]*	1.1 ± 1.9	1.5 ± 1.7	0.8 ± 1.5	0.9 ± 1.4	1.7 ± 2.0	0.6 ± 1.2	2.4 ± 1.4]**	9.0 ± 7.6]*	3.8 ± 1.8]***

mean ± SD, *: p < 0.05, **: p < 0.01, ***: p < 0.001

DISCUSSION

There have only been a few previous investigations of biochemical parameters in patients with or with-

out nocturia. These studies found an increase in natriuretic peptides (5, 10) or catecholamines (13) and a decrease in antidiuretic hormone (9) or melatonin (4) in patients with nocturia. In this study, biochem-

Table 4 Blood examination in subjects with non-bothersome ($n = 26$) or bothersome ($n = 24$) nocturnal urination \geq twice per night

Nocturnal urination \geq twice per night	Age	TP	ALB	AST	ALT	LDH
		g/dL	g/dL	IU/L	IU/L	IU/L
non-bothersome	64.7 \pm 12.9	7.4 \pm 0.5	4.4 \pm 0.2	23 \pm 9	23 \pm 16	197 \pm 52
bothersome	62.3 \pm 16.3	7.3 \pm 0.4	4.3 \pm 0.3	23 \pm 9	24 \pm 19	190 \pm 45
	CHE	T-Bil	BUN	Cre	Melatonin	AV
	IU/L	mg/dL	mg/dL	mg/dL	pg/mL	pg/mL
non-bothersome	346 \pm 67	0.4 \pm 0.2	15.1 \pm 4.2	0.8 \pm 0.2	5.4 \pm 5.3	1.7 \pm 1.0
bothersome	348 \pm 82	0.6 \pm 0.6	15.2 \pm 5.0	0.8 \pm 0.2	3.1 \pm 1.1	1.5 \pm 0.8
	Adrenalin	Noradrenalin	Dopamine	Serotonin	Blood viscosity	HANP
	pg/mL	pg/mL	pg/mL	μ g/mL	mP \cdot s	pg/mL
non-bothersome	42 \pm 23	523 \pm 281	16.7 \pm 9.3	0.02 \pm 0.01	5.46 \pm 0.88	21 \pm 15
bothersome	33 \pm 14	493 \pm 226	13.2 \pm 8.1	0.02 \pm 0.01	5.08 \pm 0.60	21 \pm 21
	BNP	WBC	RBC	Hb	Ht	Plt
	pg/mL	/ μ L	\times 10000/ μ L	g/dL	%	\times 10000/ μ L
non-bothersome	31 \pm 40	6158 \pm 1575	439 \pm 95	14.0 \pm 2.4	43.4 \pm 6.3	24.0 \pm 7.5
bothersome	30 \pm 43	6196 \pm 1728	452 \pm 50	14.1 \pm 1.7	42.6 \pm 7.8	23.6 \pm 5.7

mean \pm SD, *: $p < 0.05$ **Table 5** Urinary condition in subjects with non-bothersome ($n = 26$) or bothersome ($n = 24$) nocturnal urination \geq twice per night

Nocturnal urination \geq twice per night	Urinary frequency at daytime	Urinary frequency at nighttime	IPSS						Nocturnal urination	IPSS-total	QOL score
			Incomplete emptying	Frequency	Inter- mittency	Urgency	Weak stream	Hesitancy			
non-bothersome	7.2 \pm 3.1	2.8 \pm 0.9	1.0 \pm 1.4	1.5 \pm 1.3	1.5 \pm 2.0	1.1 \pm 1.3	1.4 \pm 1.9	1.0 \pm 1.8	2.8 \pm 0.8	10.2 \pm 6.4	2.8 \pm 1.7
bothersome	7.8 \pm 4.3	3.1 \pm 1.4	1.3 \pm 2.1	1.8 \pm 1.9	1.1 \pm 1.6	1.1 \pm 1.5	2.1 \pm 2.2	0.7 \pm 1.3	3.0 \pm 1.2	10.9 \pm 8.0	4.4 \pm 1.5

mean \pm SD, ***: $p < 0.001$

ical parameters were compared between subjects with non-bothersome nocturnal urination and those with bothersome nocturnal urination. The serum melatonin level was lower in subjects with bothersome nocturnal urination regardless of the frequency of urination (\geq once per night and \geq twice per night). In subjects with bothersome nocturnal urination \geq once per night, the urinary frequency at nighttime, the total score of the IPSS, and the QOL score were higher compared with those in subjects with non-bothersome nocturnal urination \geq once per night. However, among subjects with nocturnal urination \geq twice per night, only the QOL score was significantly higher in the subjects with bothersome nocturnal urination. The parameters of the IPSS did not differ between the subjects with and without bothersome nocturnal urination because their lower urinary tract symptoms were controlled by medication, suggesting that the main cause of the increased scores of the IPSS and the QOL in subjects with bothersome nocturnal urination was nocturia itself.

Melatonin is one of the strongest natural antioxidants and is produced by the pineal gland; it also has a close relation to sleep in humans (4). In our previous study, several biochemical parameters were measured during the daytime and nighttime in persons with or without nocturia (13), and the melatonin level was found to be significantly higher at night, with a significant correlation between daytime and nighttime melatonin levels (unpublished data). Therefore, the difference in daytime melatonin levels between the two groups in the present study is thought to reflect a difference in the nighttime melatonin level. The decrease in the serum melatonin level in subjects with bothersome nocturnal urination suggests that they may have a sleep disturbance, which is one of the main causes of nocturia, rather than the decrease in the melatonin being produced by a lack of sleep due to nocturia.

Administration of melatonin was found to improve nocturia in patients with bladder outlet obstruction (6). Administration of melatonin (3 mg/

day) for up to 6 months was reported to improve sleep quality and decrease the sleep onset latency in patients with insomnia (11). In addition to melatonin, hypnotics are reported to be useful for treating nocturia (7, 16). Fujikawa *et al.* found that minor tranquilizers are especially effective for controlling nocturia in patients with low HANP levels (7). Therefore, treatment of sleep problems is important for improving nocturia. Besides medication, walking for 30 minutes or more in the evening also decreases the number of nocturnal urinations and induces better sleep (15). The main factor related to the influence of walking on nocturia is that sleep becomes deeper, which may increase the arousal threshold bladder volume. Therefore, any therapy for sleep disturbance may also become a therapy for nocturia.

Nocturnal urinary frequency, a common symptom in the elderly, is one of the most bothersome urologic symptoms (3). However, we found that the number of subjects in the non-bothersome group was larger than in the bothersome group. Among the subjects with nocturnal urination ≥ 4 times per night, however, the number in the bothersome group was larger than that in the non-bothersome group. Therefore, simply decreasing the number of nocturnal episodes of urination is not an effective therapy for nocturia. From the present findings, nocturnal urination being perceived as non-bothersome was thought to be related to maintaining a higher level of melatonin (a sleep inducer) and obtaining sufficient sleep. Therefore, any therapy for improving sleep will also be able to improve nocturia, even if the number of nocturnal urinations does not decrease significantly.

In conclusion, nocturnal urination might be not perceived as bothersome by subjects with a high level of melatonin (a sleep inducer) in which sufficient sleep was able to be kept. When nocturia is not improved by any standard therapy to decrease the number of episodes of urination, it would be better to choose a therapy for sleep disturbance, such as the administration of melatonin/hypnotics or exercise in the evening.

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