

Benign Prostatic Hyperplasia in Community-Dwelling Elderly in Korea

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Background. This study was done to identify the prevalence of benign prostatic hyperplasia (BPH) and BPH-related symptoms among community-dwelling elderly men in Korea. In addition, quality of life and health care-seeking behavior were explored.

Methods. A total of 417 elderly men were surveyed using the IPSS (International Prostatic Symptom Score) and a structured questionnaire on health care-seeking behaviors.

Results. The prevalence of BPH was 19.7%. Of those with BPH, 80.3% reported mild symptoms, 13.2% moderate symptoms, and 6.5% severe symptoms. The severity of BPH-related symptoms was significantly correlated with quality of life. Among those with BPH, 42.7% had never consulted with anyone about their symptoms.

Conclusions. BPH has emerged as a serious public health problem in elderly men. Elderly people who experience worse symptoms of BPH have a lower quality of life. Many elderly with BPH do not seek health care, mainly due to misconceptions about BPH. The provision of educational programs for BPH may significantly improve the quality of life of elderly men.

Key Words : benign prostatic hyperplasia; elderly, Korea

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a non-cancerous enlargement of the prostate gland that occurs with normal aging (McConnell et al., 1994). Although the reported prevalence of the disease has varied widely among studies due to the lack of a standardized definition and a unified diagnostic criterion, and to differences in the samples used in community-based surveys, it is generally accepted that the prevalence of BPH increases with advancing age (Garraway et al., 1991). With the enlargement of the prostate gland, individuals experience unpleasant urinary voiding symptoms (e.g., hesitancy, weak stream, intermittence, and incomplete emptying) and storage symptoms (e.g., frequency, urgency, and noc-

turia).

The lower-urinary-tract symptoms are not indicative of a life-threatening condition, but the symptoms do interfere with daily and social activities, lead to negative emotional feelings (e.g., depression, embarrassment, and lack of control), and, finally, decrease in the quality of life (Naughton & Wyman, 1997). From the perspective of health expenditures, BPH assumes a significant share of the health care costs. In the United Kingdom, £ 62-£ 91 million is spent annually on BPH (Drummond et al., 1993), and in the USA the estimated cost exceeds US\$4 billion per annum (Kortt & Bootman, 1996). In Japan, the market for medical therapy associated with BPH is approximately 80 billion yen (Terai et al., 2000).

According to the Korea National Statistical Office (Korea National Statistical Office, 2001), the proportion

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of Koreans aged 65 years and over was 5.9% in 1995 and 7.2% in 2001, and is predicted to increase to 14.4% by 2019. With aging of the population the prevalence of BPH in elderly men is likely to increase, and hence health strategies are needed for dealing with the associated increase in BPH problems. The first, most basic information required includes the prevalence of the disease, BPH-related symptoms, its impact on life, and health care-seeking attitudes related to the disease. However, a systematic community-based study with elderly on such basic information has rarely been conducted in Korea. Therefore, the purpose of the present study was to identify the prevalence of BPH and BPH-related symptoms among community-dwelling elderly men in South Korea. In addition, the BPH-related global quality of life and health care-seeking behavior were explored.

METHODS

This study formed part of a large cross-sectional project to identify the health status of older people living in the city of Anyang in South Korea. At the time of the study, the city population of 31,875 elderly comprised of 11,967 men and 19,908 women aged 65 years or over, of which 1,298 subjects were randomly selected by the combination of age- and gender-stratified sampling with district ("Gu" and "Dong")-cluster sampling. After receiving approval for the protection of human rights from the institutional review board of the university at which the authors of this study are working, ten trained research assistants visited the homes of potential elderly subjects who had agreed to participate in this study and outlined the purpose of the study and the nature of participation to them. If they articulated an understanding of the study, they were asked to sign the consent forms, after which the research assistants interviewed them using structured questionnaires. Of the 1,298 participants, 417 elderly males without prior prostate surgery, prostate cancer, or bladder disease were included in the analyses. All the subjects included had normal scores (over 23) on the screening test of the MMSE-K (Mini-Mental State Examination - Korean version) (Park & Kwon, 1989).

The prevalence of BPH was assessed using the International Prostatic Symptom Score (IPSS), which is the most common method for estimating the prevalence of BPH in a community survey (Barry et al., 1992). The IPSS was formerly known as the American Urology

Association Symptom Index (AUA-SI). The International Consensus on Urology Disease in Paris in 1999 adopted the AUA-SI by adding one-item measuring the impact of symptoms on global quality of life, and renamed it the IPSS under the auspices of the World Health Organization (Barry et al., 1992). This questionnaire consists of three items relating to storage symptoms (frequency, urgency, and nocturia), four items on voiding symptoms (hesitancy, weak stream, intermittence, and incomplete emptying), and one item on the global quality of life. The items relating to symptoms use a 6-point Likert scale (0 meaning "none," and 5 meaning "five times or more"). The total score for symptoms was calculated by summing the scores of the seven BPH-related symptoms: the total score ranges from 0 to 35, with a higher score indicating a higher level of symptoms. The total IPSS is then categorized into three levels of severity: minor (0–7), moderate (8–19), or severe (20–35). BPH is considered to be present when the IPSS is over 7 (Barry et al., 1992). The reliability and validity of the IPSS has been established with populations in many countries, including South Korea (Choi et al., 1996). The single item on the global quality of life on the IPSS asks the subject on the continuum of satisfaction and dissatisfaction living with the urinary symptoms. The item consists of a 7-point Likert scale (0 = "very satisfied," and 6 = "terrible"), with a higher score indicating a lower quality of life. To explore health care-seeking behaviors associated with the symptoms of BPH, elderly individuals with IPSS values of over 7 were asked whether they had ever consulted others about the symptoms; if they had, the reasons for this were asked.

Data were analyzed using SPSS/PC 10.0. The data on demographics, prevalence of BPH, and health-care-seeking behavior were computed using descriptive statistics and graphs. Differences in urinary symptoms with age groups were computed using a chi-square test. The relationship of urinary symptoms to global quality of life was assessed using Spearman's rho correlation.

RESULTS

The mean age of the respondents was 70.93 years (SD = 5.04), and ranged from 65 to 84 years. The ages were grouped into 5-year intervals: 198 subjects (47.5%) were allocated to the group of 65–69 years, and 122 (29.3%), 57 (13.7%), and 40 (9.6%) subjects were allocated to groups aged 70–74, 75–79, and 80–84 years, re-

spectively. Forty-five subjects (10.8%) were widowers, and the rest were married and living with their spouses. About half of the respondents (n = 199, 47.7%) had graduated from high school, 33 subjects (7.9%) had received no education, and the remainder had graduated only from elementary or middle school.

The mean IPSS of all 417 subjects included in the study was 4.33 (SD = 7.17), and ranged from 0 to 35. The distribution was significantly positively skewed (skewness/SE skewness = 17.33), meaning that many of the elderly had lower IPSS values. Table 1 presents a frequency distribution of the percentages of symptoms severity (mild, moderate, and severe). Of all the respondents, 80.3% reported mild symptoms 13.2% moderate symptoms, and 6.5% severe symptoms. This frequency distribution of symptoms severity was classified into the age groups separated by 5-year intervals (Table 1). No significant association was found between symptom severity and age group using a chi-square test (p = 0.20).

The overall prevalence of BPH (IPSS > 7) was 19.7%. The prevalence increased from 17.6% in those aged 65-69 years to a plateau of between 22.2% and 20.0% in the other age groups (Table 1).

The mean IPSS for subjects with BPH (IPSS > 7) (Table 2) was 16.76 (SD = 7.07). The mean scores of storage and voiding symptoms were 7.66 (SD = 2.86)

and 9.10 (SD = 4.86), respectively. Of urinary symptoms, the mean score of nocturia was the highest, followed by those of weak stream, incomplete emptying, frequency, intermittence, hesitancy, and urgency.

Figure 1 presents the distribution of responses of global quality of life. Subjects who responded as “mostly dissatisfied” represented the largest group (34.1%). The global quality of life was significantly correlated with the severity of BPH-related symptoms (rs = 0.52, p = 0.000).

Of the subjects with BPH (n = 82) (Table 3), 57.3% (n = 47) had consulted with friends (n = 5), spouses (n = 5),

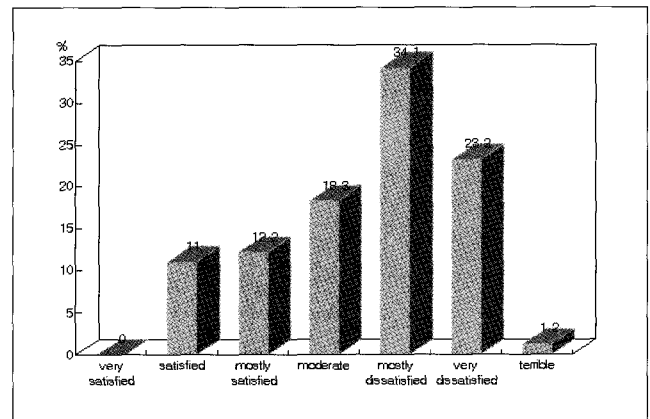


Figure 1. Distribution of quality-of-life responses for elderly men with BPH

Table 1. Frequency Distributions of Symptoms Severity and Prevalence in Relation to Age Groups in Elderly Men Aged 65 and Over

Age (years)	Symptoms severity			Total No. (%)	Prevalence
	Mild ^a No. (%)	Moderate ^b No. (%)	Severe ^c No. (%)		Moderate and severe combined No. (%)
65-69	163 (82.3)	28 (14.1)	7 (3.5)	198 (100)	35 (17.6)
70-74	95 (77.9)	13 (10.7)	14 (11.5)	122 (100)	27 (22.2)
75-79	45 (78.9)	8 (14.0)	4 (7.0)	57 (100)	12 (21.0)
80-84	32 (80.0)	6 (15.0)	2 (5.0)	40 (100)	8 (20.0)
Total	335 (80.3)	55 (13.2)	27 (6.5)	417 (100)	82 (19.7)

^aIPSS 1-7, ^bIPSS 8-19, ^cIPSS 20-35

Table 2. Mean, Standard Deviation, Range of Symptom Scores of the Elderly with IPSS Values Over 7

Symptom	M	SD	Actual range	Possible range
Storage symptoms	7.66	2.86	2.00-15.00	0.00-15.00
Frequency	2.17	1.42	0.00- 5.00	0.00- 5.00
Urgency	1.55	1.65	0.00- 5.00	0.00- 5.00
Nocturia	3.94	1.35	0.00- 5.00	0.00- 5.00
Voiding symptoms	9.10	4.89	1.00-20.00	0.00-20.00
Hesitancy	2.00	1.71	0.00- 5.00	0.00- 5.00
Weak stream	2.85	1.56	0.00- 5.00	0.00- 5.00
Intermittence	2.02	1.67	0.00- 5.00	0.00- 5.00
Incomplete emptying	2.22	1.65	0.00- 5.00	0.00- 5.00
Total	16.76	7.07	3.00-35.00	0.00-35.00

or health professionals ($n = 37$) about their BPH-related symptoms. The remaining 42.7% ($n = 35$) had never sought help because they thought the symptoms were a natural aging process and untreatable. Others felt embarrassed, or fearful of cancer.

DISCUSSION

The present study was conducted to identify the prevalence of BPH and BPH-related symptoms using the IPSS. In addition, the relationship of BPH-related symptoms severity to global quality of life and health-care-seeking behavior for the disease were explored. In this study the overall prevalence of BPH was 19.7%, which is similar to the prevalence of some community-based studies (Table 4). In the study by Lee et al. (1995) involving 519 Korean men over 50 years old, 23.2% had BPH using the IPSS. Similarly, Nacey et al. (1995) reported that the prevalence of BPH in 495 New Zealand men aged 40 and over (284 Caucasian, 85 Maori, and 137 Pacific Islanders, and 9 other ethnicity) was 23.0%. The prevalence of BPH in Canadian men has been reported at 23.0% (Norman et al., 1994). However, studies on men in the USA (Girman et al., 1994), the Netherlands (Bosch et al., 1995), the UK (Trueman et

al., 1999), and Japan (Tsukamoto et al., 1995) have reported much higher prevalences of BPH using the IPSS. The prevalence was highest in Japanese men, but this should be interpreted carefully since nonrandom sampling was used in that study - self-selection functions as a bias in study sampling that can inflate the prevalence.

The prevalence of BPH in the present study tended to be lower than the prevalence reported in other countries, but the percentage of our respondents who had severe symptoms was the highest reported, at 6.5%. This percentage is higher than that for Korean men aged 50 years and over (Lee et al., 1995), and is much higher than those for French (Saniger et al., 1995) and Canadian (Norman et al., 1994) men. These results indicate that relatively many Korean elderly are suffering from severe BPH-related symptoms.

Considering that the population of those aged 65 and over in Korea is rapidly increasing, with their proportion in the population estimated to double by the year 2019 (Korea National Statistical Office, 2001), BPH might become a serious public health problem, especially in terms of its impact on medical costs. According to the Korea Medical Insurance Corporation (Korean Medical Insurance Corporation, 1995), treatment for BPH cost 1.4 billion South Korean Won (about US\$ 1.2 million) in 1994, and increased to 21.6 billion South Korean Won (about US\$ 17.8 million) in 2001; and this increasing trend in the treatment costs for BPH may accelerate over the next decade.

In the present study, there was no significant increase in the severity of urinary symptoms with age, which is not consistent with many other studies. This discrepancy may be related to differences in the samples analyzed.

Table 3. Consultant about BPH-related Symptoms ($n^* = 82$)

Consultant	n	%
Friend	5	6.1
Spouse	5	6.1
Health professionals	37	45.1
Never consulted with others	35	42.7

* Number of subjects with BPH

Table 4. Prevalence and Symptoms Severity of BPH from Community-based Surveys Among Countries

Country	N	Sampling	Age	Instrument	Prevalence (%)	Symptoms severity (%)		
						Mild	Moderate	Severe
Korea (Present study)	417	Age- and gender-stratified random	65-84 years	IPSS	19.7	80.0	13.2	6.5
Korea (Lee et al., 1995)	519	Randomized cluster	50 years and over	IPSS	23.2	76.8	18.7	4.5
New Zealand (Nancy et al. 1995)	495	Age-stratified random	40 years and over	IPSS	23.0	77.0	18.0	5.0
Canada (Norman et al., 1994)	508	Random digit-dialing method	50 years and over	Adapted AUA-SI	23.0	77.0	21.0	2.0
USA (Girman et al., 1994)	2,115	Age- and urban/rural-stratified random	40-79 years	AUA-SI	38.0	-	-	-
Nederland (Bosch et al., 1995)	502	Random	55-74 years	IPSS	30.0	70.0	24.0	6.0
UK (Trueman et al., 1999)	1,480	Random	55 years and over	IPSS	41.0	-	-	-
Japan (Tsukamoto et al., 1995)	289	Nonrandom	40-79 years	IPSS	44.2	-	-	-
France (Saniger et al., 1995)	2,011	Random	50-80 years	AUA-SI	13.3	85.8	13.0	1.2

IPSS: International Prostatic Symptom Score, AUA-SI: American Urology Association Symptom Index

The sample subjects in the present study were aged from 65 to 84 years, while most other studies involved men aged 40 or 50 years and over. It is conjectured that the relatively homogeneous ages of the subjects in the present study is a reason for this lack of a relationship between urinary symptoms and age.

In this study, nocturia and weak stream were the most prevalent BPH-related symptoms, and urgency had the lowest prevalence. This is consistent with a previous study involving Korean men aged 50 years and over (Lee et al., 1995). Nocturia was also ranked highest in studies from New Zealand (Nacey et al., 1995), Netherlands (Bosch et al., 1995), Canada (Norman et al., 1994), and Asia and Australia (Homma et al., 1997).

In this study, the global quality of life of the elderly with BPH was measured using a 7-point Likert-scored item from the questionnaire of the IPSS. A significant moderate correlation was found in this study between the IPSS values and the global quality of life, indicating that those elderly experiencing worse symptoms have a lower quality of life.

Associated with BPH, many studies have used the global quality of life measure included in the IPSS to assess the quality of life. However, this measure is not sufficiently sensitive to detect several aspects of quality of life of elderly people with BPH. A universally unified definition of health-related quality of life does not exist, and its attributes are multidimensional, including physical, social, functional, and emotional aspects (Fayers & Machin, 2000). According to previous studies, BPH-related symptoms impact on daily and social activities, such as interfering with fluid intake before travel and bedtime, driving for longer than 2 hours, visiting places without a toilet, playing outdoor sports, and going to movies, church, or other public places (Girman et al., 1994; Garraway et al., 1993). BPH-related symptoms also influence psychological or emotional well-being and sexual satisfaction (Girman et al., 1994; Tsang & Garraway, 1993). These empirical findings imply that BPH-related symptoms are associated with several dimensions of the lives of elderly men, indicating that a multidimensional measure of BPH-related quality of life is more useful in determining which aspects of quality of life are affected by BPH-related symptoms. The WHO-QOL-Brief (1998), the Nottingham Health Profile (Hunt et al., 1981), and the SF-36 (Ware & Sherbourne, 1992) have been used to measure multidimensionally the quality of life of men with BPH. However, these instruments

were originally designed to measure a broad range of health conditions in the general population, not specific to certain conditions and populations. Therefore, to measure the quality of life of people with BPH, it is recommended that future investigations use a BPH-specific and multidimensional instrument that has established reliability and validity.

Approximately half of the elderly with BPH in this study had never consulted with others about their BPH-related symptoms, mainly because they regarded urinary symptoms as a natural aging process or as untreatable. Hunter and Berra-Unamuno (1997) also noted that a high proportion of affected men consider that BPH-related symptoms are a normal aging process, with the result that they do not tend to consult their physicians. These observations indicate that many elderly suffer from urinary symptoms due to misconceptions about BPH, and hence educational interventions should be administered to provide the elderly with the correct knowledge and to encourage them to consult with health professionals and access medical care for their BPH-related symptoms. This may increase the quality of life of elderly men.

In this study, the prevalence of BPH was solely dependent on the measurement using the IPSS - physiological and anatomical measures were not included as criteria for BPH. This may present as a limitation to the external validity of this study. Thus, it is recommended in future investigations to include other criteria, such as uroflometry or prostate volume.

CONCLUSION

In conclusion, the prevalence of BPH among Korean elderly men aged 65 and over was found to be 19.7% using the IPSS. Nocturia was the most commonly reported BPH-related symptom. Elderly persons who experienced worse BPH symptoms had a lower quality of life. About half of the elderly with BPH had never consulted with others about their BPH-related symptoms, since they had misconceptions that lower-urinary symptoms were a natural aging process or were untreatable.

References

- Barry, M. J., Fowler, F. J., Jr O'Leary, M. P., Bruskewitz, R. C., Holtgrewe, H. L., Mebust, W. K., & Cockett, A. T. K. (1992). The American Urological Association symptom index for benign prostatic hyperplasia: The measurement committee of the American Urological Association. *J Urol*, 148, 1549-1557.

- Bosch, J. H. R., Hop, W. C. J., Kirkel, W. J., & Schroder, F. H. (1995). The international prostate symptom score in a community-based sample of men between 55 and 74 years of age: Prevalence and correlation of symptoms with age, prostate volume, flow rate and residual urine volume. *J Urol*, 75, 622-630.
- Choi, H. R., Chung, W. S., Shim, B. S., Kwon, S. W., Hong, S. J., Chung, B. H., Sung, D. H., Lee, M. S., & Song, J. M. (1996). Translation validation and reliability of I-PSS Korean version. *Korean J Urol*, 37, 659-665.
- Collins, G. N., & Simpson, R. J. (1993). Impact of previously unrecognized benign prostatic hyperplasia on the daily activities of middle-aged and elderly men. *Br J Gen Pract*, 43, 318-321.
- Drummond, M. F., McGuire, A. J., Black, N. A., Petticrew, M., & McPherson, C. K. (1993). Economic burden of treating benign prostatic hyperplasia in the United Kingdom. *Br J Urol*, 71, 290-296.
- Fayers, P. M., & Machin, D. (2000). *Quality of life: Assessment, analysis and interpretation*. Wiley: West Sussex, England.
- Garraway, W. M., Collins, G. N., & Lee, R. J. (1991). High prevalence of benign prostate hypertrophy in the community. *Lancet*, 338, 469-471.
- Garraway, W. M., Mckelvie, G. B., Russell, E. B. A. W., Hehir, M., Lee, R. J., Rogers, C. A. N., Tsang, K. K., & Garraway, W. M. (1993). *Impact of benign prostatic hyperplasia on general well being of men*. *Prostate*, 23, 1-7.
- Girman, C. J., Panser, L. A., Epstein, R. S., Oesterling, J. E., Jacobsen, S. J., Lieber, M. M., & Guess, H. A. (1994). Natural history of prostatism: Impact of urinary symptoms on quality of life in 2115 randomized selected community men. *Urol*, 44(6), 825-831.
- Homma, Y., Kawabe, K., Tsukamoto, T., Yamanaka, H., Okada, K., Okajima, E., Yoshida, O., Kumazawa, J., Fang-Liu, G., Lee, C., Hsu, T.-C., Cruz, R. C. D., Tantiwang, A., Lim, P., Sheikh, M. A., Bapat, S. D., Marshall, V. R., Tajima, K., & Aso, Y. (1997). Epidemiologic survey of lower urinary tract symptoms in Asia and Australia Using international prostatic symptom score. *Int J Urol*, 4(1), 40-46.
- Hunt, S. M., McKenna, S. P., McEwen, J., Williams, J., & Papp, E. (1981). The Nottingham health profile: Subjective health status and medical consultations. *Soc Sci Med*, 15, 221-219.
- Hunter, D. J. W., & Berra-Unamuno, A. (1997). Treatment-seeking behavior and stated preferences for prostatectomy in Spanish men with lower urinary tract symptoms. *Br J Urol*, 79, 742-748.
- Korean Medical Insurance Corporation. (1995). '94 Medical Insurance Statistical Yearbook. *Korean Medical Insurance Corporation*, Seoul.
- Korea National Statistical Office. Population. (2001). *Korea National Statistical Office*, Seoul.
- Kortt, M. A., & Bootman, J. L. (1996). The economics of benign prostatic hyperplasia treatment: A literature review. *Clin Ther*, 18(6), 1227-1241.
- Lee, E. S., Lee, C., Kim, Y. S., & Sin, Y. (1995). Estimation of benign prostatic hyperplasia prevalence in Korea: An epidemiology survey using International Prostatic Symptom Score in Yonchon country. *Korean J Urol*, 36(12), 1345-1352.
- McConnell, J. D., Barry, M. J., Bruskewitz, R. C., Bueschen, A. J., Denton, S. E., & Holtgrewe, H. L. (1994). Benign prostatic hyperplasia: Diagnosis and treatment. Clinical practice guideline, Number 8. Rockville, MD, US Department of Health and Human Services. *Public Health Service*, Agency for Health Care Policy and Research.
- Nacey, J. N., Morum, P., & Delahunt, B. (1995). Analysis of the prevalence of voiding symptoms in Maori, pacific island and Caucasian New Zealand men. *Urol*, 46(4), 506-511.
- Naughton, M. J., & Wyman, J. F. (1997). Quality of life in geriatric patients with lower urinary tract dysfunction. *Am J Med Sci*, 314, 219-227.
- Norman, R. W., Nickel, J. C., Fish, D., & Pickett, S. N. (1994). Prostate-related symptoms in Canadian men 50 years of age or older: prevalence and relationships among symptoms. *J Urol*, 74, 542-550.
- Park, J.-H., & Kwon, Y.-C. (1989). Standardization of Korean version of the mini-mental state examination for use in elderly: Part II. Diagnostic validity. *J Korean Neuropsychia Asso*, 28(3), 508-513.
- Saniger, P. P., MacFarlane, G., & Teillac, P. (1995). Impact of symptoms of prostatism on level of bother and quality of life of men in the France community. *J Uro*, 153, 669-673.
- Terai, A., Kakehi, Y., Terachi, T., & Ogawa, O. (2000). National trend of management of benign prostatic hyperplasia in Japan during 1990s: Analysis of national health statistics. *Hinyokika Kyo*, 46(8), 537-544.
- Trueman, P., Hood, S. C., Nayak, U. S. L., & Mrazek, M. F. (1999). Prevalence of lower urinary tract symptoms and self-reported diagnosed 'benign prostatic hyperplasia', and their effect on quality of life in a community-based survey of men in the UK. *BJU Inter*, 83, 410-415.
- Tsukamoto, T., Kumamoto, T., Masumori, N., Miyake, H., Rhodes, T., Girman, C. J., Guess, H. A., Jacobsen, S. J., & Lieber, M. M. (1995). Prevalence of prostatism in Japanese men in a community-based study with comparison to a similar American study. *J Urol*, 154, 391-395.
- Ware, J. E., & Sherbourne, C. D. (1993). A 36-item Short-Form health survey (SF-36): Conceptual framework and item selection. *Med Care*, 30, 478-483.
- WHOQOL group. (1998). Development of the World Health Organization WHOQOL-BRIF Quality of life assessment. *Psycho Med*, 28, 551-558.