

Effect of weight reduction on the severity of lower urinary tract symptoms in obese male patients with benign prostatic hyperplasia: A randomized controlled trial

Chi-Hang Yee^{1,2}, Wing-Yee So², Sidney KH Yip², Edwin Wu², Phyllis Yau², Chi-Fai Ng¹

¹Department of Surgery, The Chinese University of Hong Kong, Hong Kong, ²Department of Surgery, Prince of Wales Hospital, Hong Kong, China

Purpose: We assessed whether weight reduction is an effective intervention for the management of lower urinary tract symptoms (LUTS) and investigated the relationship between obesity and LUTS.

Materials and Methods: This was a prospective randomized controlled trial that enrolled obese men older than 50 years with LUTS. The study period was 52 weeks. All patients received standardized alpha-adrenergic blocker therapy for the treatment of benign prostatic hyperplasia (BPH) during the run-in period. Patients were randomized to receive either a standardized prerecorded video program on the general principle of weight reduction or a comprehensive weight reduction program. Patients were assessed at different time points with symptom assessment, uroflowmetry, transrectal ultrasound, and metabolic assessment.

Results: Sixty-five patients were allocated to each study arm. After the study period, no significant difference in weight reduction was found between the two arms. When the pre- and postintervention parameters were compared, none were statistically different between the 2 arms, namely nocturia, International Prostate Symptom Score, quality of life assessment, and uroflowmetry parameters. When the whole study population was taken as a single cohort, these parameters were also not significantly different between the group with a body mass index of 25 to <30 kg/m² and the group with a BMI of 30 to 35 kg/m².

Conclusions: We found no association between obesity and LUTS. This could have been due to the less marked weight difference in our cohort. Whereas weight reduction may be an effective measure to improve LUTS, the implementation of a successful program remains a challenge.

Keywords: Exercise; Lower urinary tract symptoms; Obesity

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Lower urinary tract symptoms (LUTS) are common among middle-aged to elderly men [1]. It is increasingly recognized that the etiology of LUTS extends well beyond

prostate enlargement and bladder outlet obstruction [2]. Given that treatments with both surgery and medication have limitations, potential behavioral intervention that can safely reduce a man's need for surgical or medical therapy is worthwhile to explore. With some studies sug-

Received: 23 December, 2014 • **Accepted:** 4 February, 2015

Corresponding Author: Chi-Fai Ng

Department of Surgery, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, Hong Kong 999077, China
TEL: +852-26322625, FAX: +852-26377974, E-mail: ngcf@surgery.cuhk.edu.hk

See Editorial on page 246.

gesting that obese men are more likely to have LUTS [3,4], weight reduction could be one such intervention. Body size and composition have long been hypothesized to influence the risk of prostate hyperplasia [5]. While some data have suggested that weight gain worsens LUTS, few data are available to address whether the reverse is true, i.e., if weight loss can improve LUTS. Furthermore, the postulated relationship between obesity and LUTS remains controversial. Contradictory evidence about this relationship is present in the literature [6]. With this background, we conducted a prospective randomized controlled trial to investigate whether weight reduction would be an effective intervention for LUTS and assessed the relationship between obesity and LUTS among patients with BPH.

MATERIALS AND METHODS

This was a prospective randomized controlled trial. The study was approved by the local ethics and research committee. Written informed consent was given by all participants before entering the study. Obese men older than 50 years who attended our urology clinic for LUTS were enrolled. A standard investigation protocol that included a general clinical evaluation with digital rectal examination, transrectal ultrasound (TRUS), blood tests, prostate-specific antigen (PSA) measurement, uroflowmetry, and assessment of International Prostate Symptom Score (IPSS) and quality of life (QoL) score was performed during enrolment. Baseline medical history was documented. Details of the inclusion and exclusion criteria are listed in Table 1.

The study period was 52 weeks. Before the study, patients had been using different alpha blockers for relief of LUTS. Standardized alpha-adrenergic blocker therapy (tamsulosin 0.4 mg oral controlled absorption system) for the medical treatment of BPH/LUTS was given to all patients during the run-in period. Subjects were reassessed at 4 weeks after the run-in period for assessment of baseline parameters. After these assessments, patients were randomly assigned to receive either a standardized pre-recorded video program on the general principle of weight reduction or a comprehensive weight reduction program.

The comprehensive weight reduction program included 3 aspects, namely, an integrated assessment, a weight reduction protocol, and medical nutrition therapy. The integrated assessment included assessment of dietary and activity patterns together with appropriate counseling. Then a weight reduction protocol was devised and supervised by a registered physiotherapist with an American College of

Sports Medicine exercise specialist background. The protocol consisted of an initial stage, an improvement stage, and a maintenance stage. Concerning the medical nutrition therapy, it was formulated by dietitians to address individual needs for weight reduction.

After randomization, patients were assessed at different time points over the course of 48 weeks with symptom assessment, EuroQol visual analogue scale (EQ VAS), uroflowmetry, TRUS, and metabolic assessment. The EQ VAS is a visual scale from 0 to 100 for a patient's subjective assessment of his or her own health state. The higher the score, the better the patient perceives his health state. The follow-up protocol of the study is illustrated in Fig. 1.

With the aim of assessing the effect of a comprehensive weight reduction program on the severity of LUTS, the primary end point was a change in IPSS at the end of the trial compared with baseline. Secondary end points included change in uroflowmetry parameters, change in nocturia episodes, and change in prostate volume.

On the basis of our center's database of more than 1,000 patients with LUTS, the mean total IPSS for patients with moderate to severe symptoms is 19 with a standard deviation of 7. A sample size of 65 in each group would have 80% power to detect a 4-point difference in means, with a 0.05 two-sided significance level and a loss to follow-up rate of 30%.

Descriptive statistics were used to characterize the demo-

Table 1. Inclusion and exclusion criteria

Inclusion criteria	
Men aged ≥ 50 years old	
BMI, 25–35 kg/m ²	
Moderate to severe lower urinary tract symptoms (IPSS > 7)	
Qmax, 5–15 mL/s, PVR < 150 mL	
TRUS prostate volume > 30 mL	
Exclusion criteria	
Patients with urethral stricture, neurogenic bladder, or structural abnormality	
Patients on long-term catheterization or intermittent self-catheterization	
Patients with prostate cancer or bladder cancer	
Patients on 5 α -reductase inhibitors, phytotherapy, or hormonal therapy	
Patients who cannot tolerate tamsulosin OCAS	
Patients with poor cardiac status (NYHA class III or above) or other medical	
Conditions that are not suitable for intense exercise or weight reduction program	

BMI, body mass index; IPSS, International Prostate Symptom Score; Qmax, maximal flow rate; PVR, post-void residuals; TRUS, transrectal ultrasound; OCAS, oral controlled absorption system; NYHA, New York Heart Association.

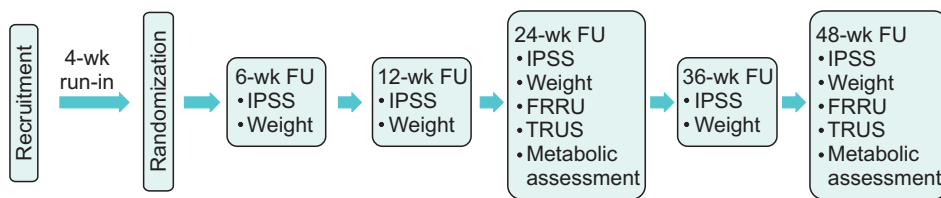


Fig. 1. Study protocol. FU, follow-up; IPSS, International Prostate Symptom Score; FRRU, uroflowmetry.

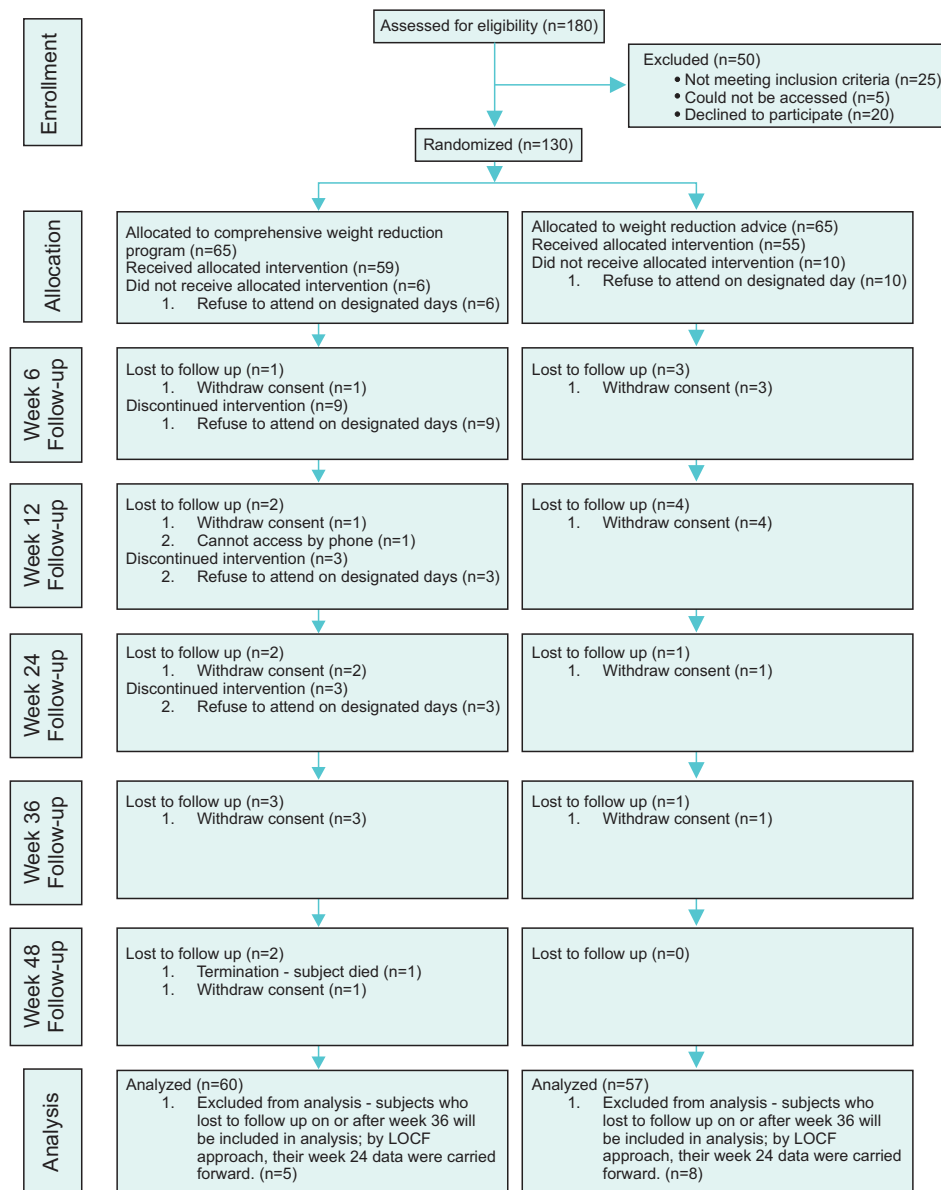


Fig. 2. Study flow diagram. LOCF, last observation carried forward.

graphic data, uroflowmetry results, prostate volume, IPSS and QoL scores, and body mass index (BMI). Comparison of continuous data between the two arms was done with t-tests or analysis of variance if the data were of normal distribution and with the Mann Whitney U test or Kruskal-Wallis test if the data were ordinal or skewed. Values of $p < 0.05$ were considered statistically significant. The IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA) was

used for all calculations.

RESULTS

A total of 180 patients were assessed for eligibility, 50 patients were excluded for various reasons, and in the end 130 patients were randomly assigned into the two study arms (Fig. 2). Sixty-five patients were allocated to

general weight reduction advice and 65 patients to a comprehensive weight reduction program. In the end, 117 patients completed the study. Patient characteristics are listed in Table 2. There were no significant differences in baseline characteristics between patients in the control arm and those in the active arm.

After the 48-week study period, we noted changes in BMI of $-0.4 \pm 0.9 \text{ kg/m}^2$ and $-0.4 \pm 0.8 \text{ kg/m}^2$ in the control arm and the active arm, respectively. The differences between the pre- and postintervention parameters were com-

pared between these two groups, namely, nocturia episodes, total IPSS, IPSS irritative score subset (sum of score of IPSS questions 2, 4, and 7), and EQ VAS. None of these parameters was significantly different between the control and active arms (Table 3).

In view of these negative results, we looked at the whole study population as a single cohort of obese men with LUTS and tried to identify whether there was a relationship between obesity and LUTS. Subjects were categorized into two groups according to their baseline BMI,

Table 2. Subject demographics and characteristics

Characteristic	Control ^a	Active ^a	p-value ^c	25≤BMI<30 (kg/m ²)	30≤BMI≤35 (kg/m ²)	p-value ^d
No. of subjects	57	60		101	13	
Mean age (y)	63.3±7.8	66.5±6.9	0.88	66.9±7.1	62.5±7.7	0.04
Weight (kg)	75.2±6.6	74.3±8.4	0.53	73.7±6.4	84.0±9.3	>0.01
Height (m)	1.66±0.05	1.65±0.07	0.51	1.65±0.06	1.64±0.08	0.39
BMI (kg/m ²)	27.4±1.9	27.3±2.0	0.51	27.0±1.4	31.2±1.5	>0.01
Nocturia episodes	2.5±1.2	2.6±1.2	0.63	2.5±1.2	2.7±1.4	0.61
Total IPSS	17.6±6.3	17.3±6.9	0.80	17.4±6.6	17.2±6.8	0.93
Irritative score ^b	7.6±3.3	8.1±2.9	0.44	7.8±3.1	8.0±3.6	0.82
IPSS QoL score	3.3±0.9	3.2±1.2	0.52	3.3±1.0	2.8±1.5	0.13
EQ VAS	73.8±15.8	74.5±13.8	0.81	75.1±14.1	65.8±18.9	0.11
Qmax (mL/s)	10.4±4.3	10.2±3.9	0.81	10.0±3.4	12.2±6.9	0.46
PVR (mL)	57.6±79.2	37.5±48.1	0.27	51.5±68.5	24.8±36.2	0.23
Prostate size (mL)	52.1±23.2	56.6±31.1	0.89	56.8±28.4	40.1±15.3	0.03
PSA (µg/L)	4.21±4.62	5.14±5.17	0.27	5.0±5.1	2.6±2.6	0.07

Values are presented as mean±standard deviation.

BMI, body mass index; IPSS, International Prostate Symptom Score; QoL, quality of life; EQ VAS, EuroQol visual analogue scale; Qmax, maximal flow rate; PVR, postvoid residuals; PSA, prostate-specific antigen.

^a:Control arm: general weight reduction advice; active arm: comprehensive weight reduction program. ^b:Irritative score: sum of score of IPSS questions 2, 4, and 7. ^c:p-value signifies the difference between the control arm and the active arm. ^d:p-value signifies the difference between different BMI groups.

Table 3. Difference between pre- and postintervention parameters

Parameter	Control ^a	Active ^a	p-value
BMI (kg/m ²)	-0.4±0.9	-0.4±0.8	0.88
Nocturia episodes	-0.1±0.9	-0.1±0.9	0.78
Total IPSS	-0.7±6.4	-1.8±6.6	0.38
IPSS irritative score ^b	-0.2±2.6	-0.6±2.7	0.35
IPSS QoL score	-0.3±1.0	-0.2±1.2	0.52
EQ VAS	0.4±14.8	-4.0±15.8	0.12
Qmax (mL/s)	-0.1±4.8	-0.2±3.7	0.92
PVR (mL)	-0.2±91.6	25.2±70.5	0.06
TRUS prostate volume (mL)	2.8±12.6	6.2±19.3	0.26
PSA (µg/L)	0.1±0.3	0.1±0.4	0.17

Values are presented as mean±standard deviation.

BMI, body mass index; IPSS, International Prostate Symptom Score; QoL, quality of life; EQ VAS, EuroQol visual analogue scale; Qmax, maximal flow rate; PVR, postvoid residuals; TRUS, transrectal ultrasound; PSA, prostate-specific antigen.

^a:Control arm: general weight reduction advice; active arm: comprehensive weight reduction program. ^b:Irritative score: sum of score of IPSS questions 2, 4, and 7.

Table 4. Correlation between different factors and BMI reduction

Variable	Group 1	Group 2	Group 3	Group 4	p-value
No. of subjects	20	21	20	20	
Total IPSS	-1.3±6.7	-0.3±6.8	-1.8±7.4	-0.1±5.1	0.83
Irritative score ^a	-0.6±1.8	0.2±2.8	-1.2±3.6	-0.4±2.3	0.43
IPSS QoL score	-0.4±0.9	0±1.3	-0.1±0.9	-0.3±1.5	0.63
Nocturia episodes	-0.3±1.0	-0.1±0.9	-0.4±1.0	0.0±0.7	0.61
EQ VAS	-4.3±16.3	-1.2±15.2	-2.2±17.4	-2.1±13.2	0.93
Qmax (mL/s)	0.3±4.6	-0.2±2.8	0.4±3.9	-0.6±3.5	0.80
PVR (mL)	24.9±75.5	34.3±84.9	26.1±61	-19.5±124.3	0.45
Prostate size (mL)	3.1±12.5	1.2±17.5	8.0±17.6	3.6±17.9	0.80
PSA (µg/L)	0.3±3.4	0.7±1.6	-0.3±1.8	1.2±4.8	0.20

Values are presented as mean±standard deviation.

Patients were categorized into 4 quartiles according to the percentage of weight reduction, with group 1 having the least weight reduction and group 4 having the most weight reduction.

IPSS, International Prostate Symptom Score; QoL, quality of life; EQ VAS, EuroQol visual analogue scale; Qmax, maximal flow rate; PVR, postvoid residuals; PSA, prostate-specific antigen.

^aIrritative score: sum of score of IPSS questions 2, 4, and 7.

namely, a BMI of 25 to <30 kg/m² and a BMI of 30 to 35 kg/m². A total of 101 subjects had a BMI of 25 and <30 kg/m², and 13 subjects had a BMI of 30 to 35 kg/m² (Table 2). When we looked at the baseline characteristics of these two groups, we did not notice any significant differences in terms of nocturia episodes, total IPSS, IPSS irritative score subset, IPSS QoL score, EQ VAS, or uroflowmetry parameters. As for prostate size, the group with a higher BMI had a relatively smaller prostate than did the group with a lower BMI (40.1±15.3 mL vs. 56.8±28.4 mL, respectively, *p*=0.03).

We further identified all subjects who had lost weight during the study period, and categorized this group of patients into four quartiles according to the percentage of weight reduction (Table 4). When we compared LUTS parameters and total IPSS across these four groups, we did not find any statistically significant differences.

DISCUSSION

A number of studies have been carried out to address the relationship between obesity and LUTS, and these have produced mixed results. Kristal et al. [7] reported that each 0.05 increase in waist-to-hip ratio (a measure of abdominal obesity) is associated with a 10% increased risk of IPSS>14 (*p*<0.003) and IPSS>20 (*p*<0.02). A similar positive correlation was also observed by Parsons et al. [4] and Mondul et al. [8]. To account for such observations, some have hypothesized that obesity may be linked to increased sympathetic nervous system activity, leading to increased irritative LUTS from smooth muscle contraction

[9]. In addition, obese men have an increased estrogen-to-testosterone ratio, which may play a role in prostatic tissue hyperplasia.

However, such a relationship was not demonstrated in our study. In our whole cohort of obese male subjects, there was no significant difference in LUTS between the group with BMI of 25 to <30 kg/m² and the group with BMI of 30–35 kg/m². Such absence of association between obesity and LUTS was also echoed in the studies by Kok et al. [10] and Wong et al. [11]. These contradictory results concerning obesity and LUTS could be in part due to the different degree of obesity in different studies. Mondul et al. [8] compared the risk of LUTS between 2 extreme BMI groups, namely BMI≥35 kg/m² and BMI 23 to <25 kg/m². However, in an average Asian population, there are relatively fewer severely obese (BMI 35 to <40 kg/m²) or morbidly obese (BMI≥40 kg/m²) men [12]. In our cohort, 101 subjects fell into the group of overweight (BMI 25 to <30 kg/m²), whereas only 13 subjects belonged to the obese group (BMI 30–35 kg/m²). Without a significant difference in BMI, a subtle relationship between obesity and LUTS might fail to be demonstrated in Asian-population-based studies, including our current study. However, it is worthwhile to note that in our cohort, although overweight and obese patients had a similar IPSS, obese patients actually had a smaller mean prostate size (40.1±15.3 mL vs. 56.8±28.4 mL, respectively). This might present a clue to the subtle relationship between obesity and LUTS.

In fact, the degree of weight change with respect to LUTS development was also discussed by St Sauver et al. [6] in their retrospective review of The Olmsted County Study

of Urinary Symptoms and Health Status among Men (OCS) and the Flint Men's Health Study. St Sauver et al. [6] reported that modest weight loss and weight gain were not significantly associated with changes in the American Urological Association Symptom Index score. Together with our study's findings, the data seem to suggest that although we cannot completely rule out the association between obesity and LUTS at the moment, a significant weight change or a significant degree of obesity might be needed to demonstrate such an association.

The limitation of this study lies in both patient recruitment and patient compliance. Most of our patients belonged to the overweight group (BMI 25 to <30 kg/m²) and a very small proportion of the subjects belonged to the obese group (BMI 30–35 kg/m²) (Table 2). This distribution might have masked the subtle difference in LUTS parameters between these two BMI groups. In our study, we failed to produce a statistically significant difference in the degree of weight reduction between the control arm and the active arm. Furthermore, there was no statistically significant BMI difference before and after the study period in either group. These findings reflected that even if weight reduction is an effective means of improving LUTS, having patients adhere to a weight loss program is a great challenge. Most trials, employing various therapeutic modalities, are plagued by subsequent weight regain. A systematic review of weight maintenance after lifestyle interventions found that approximately half of the weight lost is regained within 1 year of treatment cessation [13]. Even within weight loss trials of continual intervention, weight regain is prominent [14]. In our study, the comprehensive weight reduction program provided continuous support to our patients throughout the study period over a relatively long interval. After the initial 6 months, patients were reassessed every 12 weeks. This follow-up interval might have contributed to the low rate of success in weight reduction. To improve the success rate of a weight reduction program, more innovative measures might be needed in the future. Recently, success was reported in a trial in the setting of Scottish professional football clubs, in which 747 male football fans were recruited in a weight loss program delivered by community coaching staff [15]. This kind of protocol, which is gender-sensitized in context, content, and style of delivery, could be our future reference.

CONCLUSIONS

An association between obesity, weight loss, and LUTS

was not demonstrated in our study. This could have been due to the less marked weight difference and weight loss in our cohort. Although weight reduction might be an effective measure to improve LUTS, the implementation of a successful weight reduction program remains a challenge.

ACKNOWLEDGMENTS

This study was supported by Health and Medical Research Fund, Hong Kong Special Administrative Region Government (project number: 091 00391).

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. Yee CH, Li JK, Lam HC, Chan ES, Hou SS, Ng CF. The prevalence of lower urinary tract symptoms in a Chinese population, and the correlation with uroflowmetry and disease perception. *Int Urol Nephrol* 2014;46:703-10.
2. Bushman W. Etiology, epidemiology, and natural history of benign prostatic hyperplasia. *Urol Clin North Am* 2009;36(4): 403-15.
3. Parsons JK, Carter HB, Partin AW, Windham BG, Metter EJ, Ferrucci L, et al. Metabolic factors associated with benign prostatic hyperplasia. *J Clin Endocrinol Metab* 2006;91:2562-8.
4. Parsons JK, Messer K, White M, Barrett-Connor E, Bauer DC, Marshall LM, et al. Obesity increases and physical activity decreases lower urinary tract symptom risk in older men: the Osteoporotic Fractures in Men study. *Eur Urol* 2011;60:1173-80.
5. Wang S, Mao Q, Lin Y, Wu J, Wang X, Zheng X, et al. Body mass index and risk of BPH: a meta-analysis. *Prostate Cancer Prostatic Dis* 2012;15:265-72.
6. St Sauver JL, Sarma AV, Hollingsworth JM, Jacobson DJ, McGree ME, Dunn RL, et al. Associations between modest weight changes and onset and progression of lower urinary tract symptoms in two population-based cohorts. *Urology* 2011;78: 437-41.
7. Kristal AR, Arnold KB, Schenk JM, Neuhaus ML, Weiss N, Goodman P, et al. Race/ethnicity, obesity, health related behaviors and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. *J Urol* 2007; 177:1395-400.
8. Mondul AM, Giovannucci E, Platz EA. A prospective study of obesity, and the incidence and progression of lower urinary

- tract symptoms. *J Urol* 2014;191:715-21.
9. Giovannucci E, Rimm EB, Chute CG, Kawachi I, Colditz GA, Stampfer MJ, et al. Obesity and benign prostatic hyperplasia. *Am J Epidemiol* 1994;140:989-1002.
 10. Kok ET, Schouten BW, Bohnen AM, Groeneveld FP, Thomas S, Bosch JL. Risk factors for lower urinary tract symptoms suggestive of benign prostatic hyperplasia in a community based population of healthy aging men: the Krimpen Study. *J Urol* 2009;181:710-6.
 11. Wong SY, Woo J, Leung JC, Leung PC. Depressive symptoms and lifestyle factors as risk factors of lower urinary tract symptoms in Southern Chinese men: a prospective study. *Aging Male* 2010;13:113-9.
 12. El-Sayed AM, Scarborough P, Galea S. Ethnic inequalities in obesity among children and adults in the UK: a systematic review of the literature. *Obes Rev* 2011;12:e516-34.
 13. Barte JC, ter Bogt NC, Bogers RP, Teixeira PJ, Blissmer B, Mori TA, et al. Maintenance of weight loss after lifestyle interventions for overweight and obesity, a systematic review. *Obes Rev* 2010;11:899-906.
 14. Wadden TA, Neiberg RH, Wing RR, Clark JM, Delahanty LM, Hill JO, et al. Four-year weight losses in the Look AHEAD study: factors associated with long-term success. *Obesity (Silver Spring)* 2011;19:1987-98.
 15. Hunt K, Wyke S, Gray CM, Anderson AS, Brady A, Bunn C, et al. A gender-sensitised weight loss and healthy living programme for overweight and obese men delivered by Scottish Premier League football clubs (FFIT): a pragmatic randomised controlled trial. *Lancet* 2014;383:1211-21.

EDITORIAL COMMENT

Recently, obesity has become a significant male health issue that is linked to several diseases such as hypertension [1], coronary heart disease [2], diabetes [3], and dyslipidemia [4]. However, the relationship between obesity and benign prostatic hyperplasia/lower urinary tract symptoms (BPH/LUTS) remains controversial [5]. In the present study, the authors provide significant information to further our understanding of this issue. However, several limitations of the study should be noted.

This is a prospective clinical study dealing with the role of weight reduction in LUTS. The authors intended to assess if weight reduction in obese patients with LUTS might improve their symptoms. However, the comprehensive weight reduction program did not work sufficiently to reduce the weight of the participants, so the authors could not obtain any significant results from the data. In addition, the effect of the program was not validated. Furthermore,

there were few truly obese patients in the study population; therefore, no association between body mass index (BMI) and severity of LUTS was identified.

Patients without weight reduction should have been excluded from the study at a particular follow-up point, and the compliance or effectiveness of the weight reduction program should have been considered when calculating the sample size.

Regarding the definition of obesity, the World Health Organization Regional Office for the Western Pacific and the International Association for the Study of Obesity and the International Obesity Task Force published provisional recommendations for adults for the Asia-Pacific region in February 2010. These guidelines defined overweight as a BMI ≥ 23 kg/m² and obesity as a BMI ≥ 25 kg/m² [6]. However, the current study applied the criteria used for western participants to its Asian population. As a result, most participants were defined as overweight, and the number of participants defined as obese was too small to achieve statistical power. Before beginning the study, the patient demographics should have been determined using a preliminary investigation or a review of previous studies.

Though I and reviewers raised some concerning issues, I am sure that this study is valuable for the advance of research on obesity and BPH/LUTS. Both scientific interest and originality should be highly rated.

Hyun Jun Park

Department of Urology, Pusan National University Hospital, Pusan National University School of Medicine, 179 Gudeok-ro, Seo-gu, Busan 602-739, Korea
E-mail: joon501@naver.com

REFERENCES

1. Soltani Z, Washco V, Morse S, Reisin E. The impacts of obesity on the cardiovascular and renal systems: cascade of events and therapeutic approaches. *Curr Hypertens Rep* 2015;17:520.
2. Kwan AC, May HT, Cater G, Sibley CT, Rosen BD, Lima JA, et al. Coronary artery plaque volume and obesity in patients with diabetes: the factor-64 study. *Radiology* 2014;272:690-9.
3. Al-Goblan AS, Al-Alfi MA, Khan MZ. Mechanism linking diabetes mellitus and obesity. *Diabetes Metab Syndr Obes* 2014;7:587-91.
4. Mulhall J, Teloken P, Brock G, Kim E. Obesity, dyslipidemias and erectile dysfunction: a report of a subcommittee of the sexual medicine society of North America. *J Sex Med* 2006;3:778-86.

5. He Q, Wang H, Yue Z, Yang L, Tian J, Liu G, et al. Waist circumference and risk of lower urinary tract symptoms: a meta-analysis. *Aging Male* 2014;17:223-9.
6. Nanan DJ. The obesity pandemic: implications for Pakistan. *J Pak Med Assoc* 2002;52:342-6.