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REVIEW

Frailty and benign prostatic hyperplasia: The thrilling underlying impact

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Summary

Background: *World population is aging. The number of individuals aged over 65 are expected to be 71 million only in the US. 43% of this population will be men. Benign prostatic hyperplasia (BPH), defined as the benign neoplasm of the prostate gland affects 8% of men by their forties, but 90% of men over 90 years old. Lower urinary tract symptoms (LUTS) can be caused by an enlarged prostate, and it seems to be associated more with older and frailer individuals.*

Methods: *The purpose of this study is to review the potential interplay between frailty syndrome and benign prostatic hyperplasia. A thorough MEDLINE/PubMed non-systematic literature review was conducted from 1990 to March of 2022. The terms used for the search were "frailty and benign prostatic hyperplasia" and "low muscle mass and benign prostatic hyperplasia".*

Results: *It seems that, frailty poses a negative impact on the prognosis of patients with BPH, as it is associated with increased incidence of LUTS. In addition, frailty seems to be a strong predictor concerning surgical procedure failure and mortality following invasive procedures for BPH. Prostatic stent placement on the other hand appears to be the ideal solution for frail patients.*

Conclusions: *BPH has a strong association with frailty and increasing age.*

KEY WORDS: *Frailty; Benign prostatic hyperplasia; Transurethral resection of the prostate; Transurethral laser induced prostatectomy; Prostatic stent.*

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is the normal histological process of prostate gland enlargement due to aging and can lead, in many cases, to bladder outlet obstruction (1-3). In that case, BPH in older men can cause *lower urinary tract symptoms* (LUTS) which can be treated, in the early stages, by medications (1, 2). One third of men older than 75 years old with newly diagnosed LUTS will begin pharmacotherapy for BPH (1, 3). BPH is common in older men, as 21% of men aged over 70 years old can experience nocturia, 22% can experience the feeling of incomplete bladder emptying and 57% a decrease in urinary stream pressure (4, 5).

Combination therapy with alpha-adrenergic receptor antagonists (a-blockers) plus 5-alpha reductase inhibitors is the standard medical therapy for BPH, since the trial *Medical Therapy for Prostatic Symptoms* (MTOPS) exhibited lower rates of BPH clinical progression in individuals who received this pharmacotherapy *versus* those who received placebo (1, 6).

Pharmacotherapy can be associated with adverse drug events, which can be harmful especially in frail individuals, such as orthostatic hypotension, falls, depression and suicidal ideation (1, 7-11).

Alpha-blockers act by decreasing smooth muscle tone in the prostate gland and bladder neck, while 5-alpha reductase inhibitors act by decreasing the volume of the prostate (1, 12). Thus, the use of 5-a reductase inhibitors is not indicated in patients with low-volume prostate glands, as they will not have any particular benefit (1). Frailty, is a clinical syndrome that can lead to increased side effects of pharmacotherapy and more rapid symptom progression, thus altering the balance of the potential harms and benefits of each intervention undertaken (1, 2, 13, 14).

LUTS, affecting more than 50% of the male geriatric population, lead to a reduced quality of life and increased risk of falls, thus contributing to overall mortality (15-18). LUTS in the elderly population can be multifactorial, having as causality non urologic causes including psychosomatic manifestations (16, 19).

The difficulty of diagnosing and treating this urologic syndrome has been the hallmark of the effort to associate this complex entity with a novel age related risk factor, namely frailty (16).

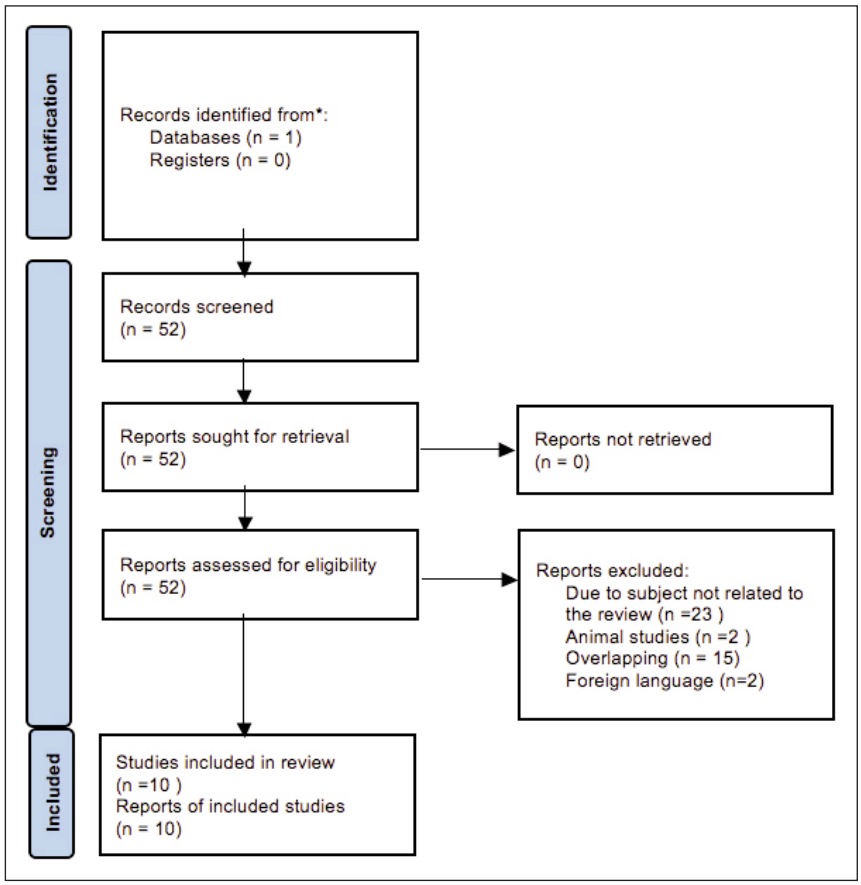
METHODS

In this non-systematic review, *PubMed* and *MEDLINE* databases were thoroughly searched from 1990 to March of 2022, using the terms: "*benign prostatic hyperplasia*" AND "*frailty*" OR "*decreased muscle mass*". Databases were screened independently by one author and rechecked by other two authors. Any disputes were solved by a fourth author (Figure 1).

From the studies screened, the original studies, as shown in Table 1, were used in order to conduct the investigation of the potential interplay between the two entities under evaluation. Studies concerning animal models were excluded.

No conflict of interest declared.

Figure 1.
Flow chart.



Results

According to *Bauer et al.* frail patients were more likely to have higher *American Urological Association Symptom Index* (AUASI) scores ($p < 0.001$) (both in voiding and storage sub-scores), higher maximum flow rate ($p = 0.02$) and decreased post-void residuals ($p < 0.01$) compared with robust individuals (1). Serum PSA ($p = 0.61$) and prostate volume ($p = 0.15$) were comparable between the groups (1). Frail individuals experienced more pronounced *adverse events* (AEs) from medications, which can stem from their overall worse status (higher body mass index-BMI), worse systolic blood pressure, worse physical and mental health, polypharmacy) ($p < 0.01$) in comparison with robust men of the same chronological age (1). Frailty was not associated with risk for BPH progression randomized in placebo or finasteride monotherapy (1). However, in the group receiving doxazosin monotherapy, frailty and pre-frailty seems to be more associated with clinical BPH progression, as proven by the increased rates of indwelling catheters or acute urinary retention episodes (aHR: 2.64; 95%; CI: 0.86-7.1) (1).

In another study of *Bauer et al.*, an association between phenotypic frailty and LUTS severity was demonstrated (3). In this study, the authors exhibited that the prevalence of moderate and severe LUTS was 46% and 13% respectively in frail men compared to 37% and 5% in robust men (moderate LUTS: HR: 1.4; 95%; CI: 1.1-1.7) (severe LUTS: HR: 2.5; 95%; CI: 1.8-3.6) (3). Those data were independent concerning the age, comorbidities or LUTS treatment and persisted among men who did not experience urinary incontinence (3). Compared to mild LUTS, the risk for mobility limitation was increased in people with moderate (HR: 1.35; 95% CI: 1.12-1.63) and severe LUTS (HR: 1.98; 95%; CI: 1.48-2.64) (20). Patients with severe (HR: 1.62; 95%; CI: 1.07-2.43) and moderate LUTS (HR: 1.32; 95%; CI: 1.05-1.67) experienced more restrictions in daily activities (20). LUTS were not associated with limitation of cognitive tasks (20). In addition, another study by the same author demonstrated that the prevalence of frailty was higher in severe and moderate LUTS (7%, 11% and 18% for mild, moderate and severe LUTS respectively) (21).

Similarly, in a Korean population study by *Jang et al.*, phenotypic frailty was prevalent in 43% of men with severe LUTS and in 16% and 7% of men with moderate and mild LUTS respectively (22).

According to *Bauer et al.*, frail patients could be diagnosed more frequently with BPH (22% *vs* 14% in non-frail individuals), overactive bladder (OAB) (25% *vs* 11% in non-frail individuals) and mixed BPH/OAB (16% *vs* 12% in non-frail individuals) (16). Moreover, people with BPH were 1.7 times more likely to be assessed as frail (OR: 1.70; 95%; CI: 1.14-2.55) with the TUGT (Timed Up to Go Test) test (16).

According to *Soma et al.* frailty was positively associated with LUTS (HR: 2.13; 95%; CI: 2.48-3.06), OAB (HR: 2.07; 95%; CI: 1.31-3.29) and higher prevalence of nocturia (23).

According to *Eredics et al.*, intraoperative complications, duration of postoperative catheterization and length of hospitalization was identical in frail and non-frail patients undergoing *transurethral resection of the prostate* (TURP) (24). However, success rate of surgery was 80.6% in fit and 75% in frail patients, while 3-month success rates were 95.2% and 83.3% for non-rail and frail respectively (24). *Post-Void Residual* (PVR) was less than 50 ml in both cohorts (24).

Pichon et al., showed that frail patients had lower success rate at 3 months (55%) compared to non-frail patients (95%) ($p < 0.05$) following TURP (25). The immediate postoperative success rate was 85% *vs* 41% in non-frail and frail cohorts respectively (25). Higher morbidity was also noted in the frail groups compared to the control group (44% *vs* 15%) ($p < 0.05$) (25).

Suskind et al., demonstrated that 95% of nursing home patients who underwent de-obstructive surgery (TURP or *Transurethral Laser Induced Prostatectomy*-TULIP) were re-catheterized at 12 months, whilst 30% of them have passed away (26).

Table 1.
Studies concerning the potential interplay between BPH and frailty.

Authors (ref)	Year, study	Study population	Findings	Exclusion criteria	Frailty assessed by:	BPH/LUTS progression assessed by:
Bauer (1)	2021, RCT	3047 men, who were treated with doxazosin monotherapy, finasteride monotherapy, placebo or combination	Frailty independently associated with BPH clinical progression and AEs	Anticholinergic except glaucoma	FI containing 68 potential deficits	AUASI scale (LUTS progression, acute urinary retention, urinary incontinence, UTI or sepsis, increase of serum creatinine at least 1.5 mg/dl attributable to BPH)
Bauer (16)	2021, prospective	2026 men over 65 years with BPH, OAB, mixed BPH/OAB	Higher incidence of those diagnosis in frail patients	Cancer, Neurologic Disease, Indwelling Catheter, Continuous Incontinence	TUGT	Based on database diagnosis divided into BPH, OAB, mixed BPH/OAB
Bauer (20)	2021, retrospective	2716 men ≥ 71 years	vLUTS severity is associated with mobility and ADL limitations among older men	Baseline self-reported functional limitations	1. Mobility (2-3 blocks or 10 steps) 2. ADL (any difficulty bathing, showering or transferring) 3. Cognition	AUASI
Eredics (24)	2020, retrospective	54 patients ≥ 75 years who underwent TURP	Fit patients benefit from TURP while frail do not	Not mentioned	7 item CHSA frailty scale	Already diagnosed
Sethi (27)	2017, retrospective	144 patients with obstructive urinary symptoms or indwelling catheter who had a Memokath stent inserted	Prostatic stent is superior to TURP for frail patients	Not mentioned	Not mentioned- Physician or anesthesiologist assessment/ not suitable for TURP	Already diagnosed
Bauer (21)	2020, retrospective	5,979 men ≥ 65 years	Higher incidence of phenotypic frailty among elderly with moderate and severe LUTS	Not mentioned	Cardiovascular Health Study Index (low mean mass, weakness, exhaustion, slowness and low physical activity)	AUASI score
Jang (22)	2018, cross-sectional	492 men ≥ 65 years and were ambulatory	The prevalence of frailty and other geriatric conditions higher in those with severe urologic symptoms	Patients living in a nursing home, hospitalized or bed riden	Frailty phenotype (exhaustion, inactivity, slowness, weakness and weight loss)	IPSS questionnaire
Soma (23)	2019, retrospective	710 people ≥ 60 years	People with LUTS more frail	Not mentioned	FP, FDS, mFI	IPSS questionnaire
Pichon (25)	2017, prospective	60 patients ≥ 60 years who underwent TURP	Patients without urinary catheter, patients with prostate cancer, PSA > 15 ng/ml ,patients unfit for anesthesia, patients with prior prostatic surgery	Geriatric assessment can predict the outcome of TURP in the elderly	BGA, CGA	Already diagnosed
Suskind (26)	2016, retrospective	2869 nursing home residents aged ≥ 65 years who underwent TURP or TULIP	Poor baseline functional status and having foley catheter preoperative is associated with higher risk of TURP or TULIP failure	Not mentioned	ADL, survival after surgery, foley catheter status	Already diagnosed

RCT: Randomized Control Trial; BPH: Benign Prostatic Hyperplasia; AEs: Adverse Events; FI: Fried Index; AUASI: American Urological Association Symptom Index; UTI: Urinary Tract Infection; OAB: Overactive Bladder; TUGT: Timed Up to Go Test; ADL: Activities of Daily Living; TURP: Transurethral Resection of the Prostate; CHSA: Canadian Study of Health And Aging; IPSS: Internation Prostate Symptom Score; FP: Frailty Phenotype; FDS: Frailty Discriminant Score; mFI: modified Frailty Index; BGA: Brief Geriatric Assessment; CGA: Comprehensive Geriatric Assessment; TULIP: Transurethral Laser Induced Prostatectomy.

According to *Sethi et al.*, prostatic stent placement is more advantageous in frail patients with *Bladder Outlet Obstruction* (BOO); 62.5% of the patients had a significant PVR difference with 550 ml before the procedure and 80 ml postoperatively respectively ($p < 0.0001$) (27). Two thirds of those patients continued to void without assistance (27); 37.5% experienced procedure failure with stent migration, occlusion, urinary retention refractory to the procedure and irritative voiding symptoms (27).

Discussion

According to this non-systematic narrative review we concluded that it seems to be an increased incidence of frailty in the elderly patients experiencing severe and moderate LUTS, as measured by the AUASI and *International Prostate Symptom Score* (IPSS) scales. Frail catheterized patients, undergoing TURP or TULIP, have higher incidence of re-catheterization or even death. Prostatic stents seem to have higher success rates in the frail and elderly.

Most of the studies included in this systematic review have large sample number. However, there are certain limitations. These studies may include heterogeneous population and use different tools of frailty quantification. Most of the studies were observational, retrospective, and non-randomized, except one. Even this study did not randomize patients based on frailty. All the aforementioned factors, necessitate the implementation of a larger multicenter randomized survey that uses a common tool for frailty assessment. Increased age is one of the most common risk factors for LUTS (16, 28). Although LUTS coexist with frailty, it is unknown which condition preexists, although many theories have been suggested for each temporal direction (16). With increasing age, several genitourinary and neural changes coexist, that can lead to decreased bladder capacity and increased bladder sensation (16, 29). LUTS can interfere with daily routine

and daily exercise thus increasing the risk of frailty (16, 30, 31). LUTS and frailty can be caused by a common mechanism, which includes insulin resistance and increased inflammatory markers, which are probably associated with LUTS progression (16, 32, 33). Aging is associated with an increase in fat mass and decline of muscle mass and strength (34, 35). Muscle mass decreases 35% between the age of 20 and 80 years old (34). Loss of strength can subsequently lead to physical function impairment and increased vulnerability (34, 36).

Multimorbidity is a common trait among the geriatric population (37). Frailty can be defined as the accumulation of health deficits and functional problems which are thought to lead to greater susceptibility to physical stressors (1). This is caused by the depletion of body physical reserves (1). Frailty can encompass also cognitive and psychosocial changes associated with many conditions (1). According to a recent medical consensus, frailty is defined as "*a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death*" (1).

Although frailty encompasses chronological age in its definition, it is a more accurate marker of biological age (1). Associations between chronological age and BPH are well established. However, associations between BPH and frailty or even biological age have been scarce till now (1). The most common clinical characteristics of frailty include weakness and slowness, which are usually associated with storage LUTS in older women (16).

Frailty preponderance is 36-88% depending of the measurement used (4). There are many tools and indexes used to assess frailty. One of the most common tools was developed by *Fried et al.* (4). This assessment concerns the frailty phenotype and is based on the cardiovascular health study. This model assesses muscle mass decline, strength, endurance, balance, walking performance and low physical activity (4). Other indexes and scores of frailty used are the *Frailty Index of Accumulative Deficits* (FI-CD), the *Geriatric 8 score* (G8 score), the simplified *Five-item Index* (sFI), the *American Society of Anesthesiologists* (ASA) physical status classification, the *Mini-Cognitive test* (mini-COG), the *Clinical Frailty Scale* (CFS), the *Eastern Cooperative Oncology Group* (ECOG) performance status, the *Cumulative Illness Score Rating-Geriatrics* (CISR-G), the *Charlson Comorbidity Index* (CCI), the *Study of Osteoporotic Fractures* (SOF) index, the "*Fatigue, Resistance, Ambulation, Illness, Loss of Weight*" (FRAIL) index, the *Comprehensive Geriatric Assessment* (CGA) and the *Multidimensional Prognostic Index* (MPI) (38-41).

There has been a novel effort in hypogonadal frail patients to reduce the frailty symptoms with the use of testosterone replacement therapy (34, 42, 43). However, testosterone use is not devoid of complications with more striking negative effects on cardiovascular system quite possibly due to polycythemia (34, 42, 43). The hypothesis for increased probability for prostate cancer on testosterone replacement therapy has not yet been proven (34, 42, 43). Novel compounds termed *selective androgen receptor modulators* (SARMs) that act selectively on androgen receptor could revolutionize testosterone replacement therapy (2). It seems they could provide the anabolic effects without the possible complications (2). However, more studies are needed to validate this.

Conclusions

Older men presenting with non-neurogenic LUTS to a urology clinic are more likely to be frail. Frailty is a systemic marker of biological age that can possibly mediate a good association between chronological age and symptoms of BPH. Currently, frailty and other markers of increased biological age are not targeted by any intervention meant for BPH, as most of them take into account only the mechanism of prostatic obstruction. The only intervention with clinical benefit could be prostatic stent placement. Therefore, screening older men with LUTS using simple tests and indexes, would be appropriate when the presence of frailty could change the diagnosis or even the treatment. This approach could lead to the development of new therapeutic strategies incorporating specific measures targeting frailty per se such as physical activity, nutritional intervention or even individually tailored geriatric models.

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