Review

Prostate- Specific Antigen (PSA) Significance in Frail Men

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Prostate- Specific Antigen (PSA) Significance in Frail Men

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Abstract: Objectives: With this study we present, for the first time to the best of our knowledge, the implications of PSA tests on the lives of frail men. **Methods**: We searched the available literature for studies analyzing the role of PSA as a screening and prognostic tool for prostatic diseases in frail men, using keywords: Prostate-specific antigen, Frailty, Prostate cancer screening, Hypogonadism and Benign Prostatic Obstruction (BPO). **Results:** PSA in frail men with more than 15 years life expectancy can detect prostate cancer in curable stages, while it enables monitoring response to different prostate cancer treatments and follow-up of testosterone replacement for hypogonadism. PSA also predicts clinical progression of patients with BPO. However, PSA is widely being offered, without personalized patient evaluation, adding to the financial burden of healthcare systems. **Conclusion:** A frailty assessment of men for the potential benefit of PSA tests on their quality of life can reduce unnecessary costs.

Keywords: prostate-specific antigen; frailty; prostate cancer screening; hypogonadism; Benign Prostatic Obstruction

1. Introduction

Prostate specific antigen (PSA) is a protease widely utilized as a screening tool for the diagnosis and follow up of patients with Prostatic Adenocarcinoma. It is well established in most healthcare systems that screening for prostate cancer with regular PSA measurements is not beneficial for elderly men with a life expectancy of less than 15 years. Thus PSA is not indicated as a marker for prostate cancer in individuals older than 75 years, unless they are symptomatic and prostate cancer is suspected. Furthermore, PSA is widely used to monitor frail patients undergoing androgen replacement treatment for hypogonadism and androgen deprivation treatment for locally advanced and metastatic prostate cancer [1–3].

This is the first review article, to the best of our knowledge, to present the application of PSA as a screening test in the population of frail individuals and the association of PSA levels with the health status of frail men.

2. Methods

We performed a non-systematic search of the available literature on PubMed, Google Scholar and Cochrane databases for studies analyzing the role of PSA as a screening and prognostic tool for prostatic diseases such as prostate cancer and benign prostatic obstruction in frail men. We used the keywords: Prostate-specific antigen, Frailty, Prostate cancer screening, Hypogonadism and Benign Prostatic Obstruction. We excluded studies not associated with frail or elderly patients and studies not written in English. Outcomes of this review were to determine the importance of PSA screening in frail men and the associated costs for the health-care system, as well as to clarify the role of PSA

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tests for the follow up of frail men treated for frailty-related hypogonadism, of the clinical progression of benign prostatic obstruction and of the treatment of local, locally advanced and metastatic prostate cancer.

2.1. PSA Screening in Frail Men

It has been shown by some studies that frail patients in European countries like Ireland and France, are less likely to have PSA tests. More significantly patients with impaired cognition, pre-frail status, low grip strength, low gait speed and low levels of physical activity were less likely to be offered regular PSA screening. However, the same studies show that people with milder coexisting morbidities such as angina, high cholesterol, hypertension are more likely to get PSA tests, potentially because of more frequent visits to healthcare facilities [4,5].

A potential explanation is that physicians avoid PSA tests in patients with very poor health, but still screen patients with milder conditions who are not frail. Furthermore, middle aged patients with severe frailty and chronic illness are also less likely to get screened for prostate cancer with PSA tests [4,5].

On the contrary, a cohort study of more than half a million veterans 70 years or older in the United states of America, showed that men with poorer health and frailty were tested equally, and in some age groups, more than younger veterans. In veterans 85 years and older for example PSA screening for men with good health was 34% and for those with worst health higher at 36% [6].

However, a more recent study in men over 75 years of age, showed that frail patients were actually significantly less likely to get PSA tests than healthy men of the same age. More specifically, 65% of men with a life expectancy of more than a decade had PSA tests, while their frail peers only had recent screening at 42%. The study concludes that the percentage of very frail individuals that are getting PSA tests is still relatively high adding to the financial burden of the healthcare system [3].

Another study used a frailty model to prove that PSA testing has led to a younger age and higher percentage of diagnosis of prostate cancer in susceptible patients such as those with a family history of the malignancy [7].

In general it seems that most studies are in agreement with the cutoff suggested by the European Association of Urology guidelines for prostate cancer screening. Hence, screening with PSA tests should depend not only on the age of men, but mainly on their life expectancy and performance status. Thus frail patients with a life expectancy of less than 15 years are unlikely to benefit from regular PSA tests [1].

2.2. PSA Levels and Health Status of Frail Patients

It is well established that PSA rises with age, mainly due to the fact that the size of the prostate increases in the aging male. PSA levels also vary in men from different ethnic groups. Other conditions such as benign prostatic enlargement and lower urinary tract infections may also affect the results of PSA testing of frail patients. Men with higher PSA could potentially have worse benign prostatic enlargement and worse lower urinary tracts symptoms affecting their quality of life [1,8,9].

PSA can predict clinical progression of Benign Prostatic Obstruction (BPO) and the risk of acute urinary retention and need for BPO-related surgical treatment. Patients with worse symptoms related to BPO tend to have higher PSA and larger prostate volumes [8]. Frail men with BPO and high residual urine also suffer from recurrent Urinary tract infections, which can also increase PSA and thus any active infections should be treated properly before an accurate PSA test can be sent [8].

Although there is a proven connection between age and PSA levels, there are no studies indicating that frailty directly affects PSA. However, hypogonadism is very common in older men and as such treatment with Testosterone may improve the quality of life of frail individuals. Testosterone has been found to improve grip strength, and increase hemoglobin[10]. Nevertheless, it should be used cautiously since it is associated with increased cardiovascular risks and abnormal levels of hematocrit and is contraindicated in men with evidence of active prostate cancer.

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Hence frail men who receive Testosterone treatment for hypogonadism should have their PSA closely monitored [11]. On the contrary, PSA cannot be used as a reliable clinical marker for male hypogonadism [12].It is important to mention that testosterone treatment for hypogonadism in the frail, has not been shown to significantly change the PSA levels and the benefits of the treatment such as on muscle strength, lean mass and quality of life in frail men, are not maintained 6 months after cessation of testosterone [10,13].

Testosterone replacement therapy may be especially beneficial for hypogonadal frail men with obesity in combination with lifestyle therapy, by improving sexual health and capacity for aerobic exercise, while minimizing muscle loss and without significantly affecting PSA levels [14].

An alternative treatment for androgen deficiency in older men is the Human chorionic gonadotropin (hCG), which increases testosterone as well as estradiol and other testicular steroids. While not affecting PSA levels. However, after 3 months of treatment, there were no significant effects on muscle strength and physical functioning [15].

PSA levels are also widely used to monitor the effectiveness of Androgen Deprivation treatment (ADT) on frail men with metastatic prostate cancer [2]. Studies use PSA monitoring to determine whether novel hormonal therapies such as Abiraterone acetate are effective on populations of elderly frail men. Abiraterone acetate has shown favorable clinical outcomes and almost 50% PSA response rate, in a cohort study of frail octogenarians that have already received docetaxel for metastatic castration- resistant prostate cancer. Toxicity was also not significantly worse than for younger age groups [16].

A placebo-controlled study showed promising results with administering liver-targeted testosterone treatment (LTTT) to frail men receiving ADT for prostate cancer. LTTT can prevent loss of muscle and bone mass during ADT without increasing peripheral blood testosterone levels. Mean PSA was not significantly affected during this treatment, apart from a few drop- outs all of whom had their PSA levels returning to initial levels. The optimal dose of LTTT needs to be determined with further studies [17].

2.3. Cost-Effectiveness of PSA Tests in Frail Individuals

It is well established that PSA screening is not beneficial for men with a life expectancy of less than 15 years [1]. This limit is mainly influenced by performance status and frailty rather than age of men alone. Apart from lack of survival benefit with PSA tests in the frail, it has been shown that screening in men above the age of 70, significantly increases the costs to the health care system (13,8% for each 5-percentage increase in screening) [18].

A Cost-utility analysis study suggests that PSA regular tests are a financial burden for healthcare systems and should be replaced by an initial PSA test at age 50 and subsequently test only patients with clinical suspicion of prostate cancer [19]. Especially for frail men 70 years or older, PSA tests were significantly associated with unnecessary expenditures due to high-cost follow up services, such as imaging, and treatments with curative-intent [20]. Hence, a reduction in PSA tests in frail individuals that will not benefit from curative treatment of prostate cancer, will decrease health care costs and at the same time improve quality of life of elderly and frail patients.

3. Conclusion

Prostate Specific Antigen is a very useful screening and prognostic tool for frail men. If used appropriately it can lead to early diagnosis of prostate cancer in frail individuals with a life expectancy of more than 15 years. It can also facilitate the instigation of the most suitable treatment for frail men with metastatic prostate cancer, as well as monitor the safety of testosterone treatment for hypogonadism in frail men with a past history of prostate cancer. A frailty assessment should determine whether an individual with comorbidities will benefit from PSA tests, to reduce financial burden of the healthcare system.

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