International Journal of Current Research and Applied Studies, (IJCRAS)

ISSN: 2583-6781

available at https://ijcras.com/

Volume 1 Issue 4 September-October 2022

Page 18-26

PATHOPHYSIOLOGY AND MANAGEMENT OF BENIGN PROSTATIC HYPERPLASIA

Gudisa Bereda

Department of Pharmacy, Negelle Health Science College, Guji, Ethiopia

ABSTRACT

Benign prostatic hyperplasia can be arising in the periurethral and transition zones of the prostatic gland and represents an inescapable phenomenon for the ageing male population. Benign prostatic hyperplasia can be described as a common and age-related disease as it is estimated that about 50% of men over the age of 50, and 80% of those older than 70 suffer from it. The risk factors for benign prostatic hyperplasia involve metabolic syndrome, diabetes, obesity, hypertension, diet and sex hormone levels. The histopathology of benign prostatic hyperplasia characteristically involves of a dual hyperplasia of the epithelial and stromal compartment of the transitional zone of the prostate. The medical managements broadly used today for treatment of benign prostatic hyperplasia are targeted to diminishing bladder outlet obstruction in order to decrease prostate volume and relax prostate smooth muscle tension. Alpha-1-blockers are considered as the first-line treatment and are used in the presence of moderate-to-severe symptomatology. Terazosin and doxazosin are non-specific alpha-1 receptor blockers confirmed for hypertension, as well as benign prostatic hyperplasia.

Keywords: Benign prostatic hyperplasia; Management; Pathophysiology

INTRODUCTION

Benign prostatic hyperplasia (BPH) can be characterizes a proliferative process of the cellular elements of the prostate, an enlarged prostate, or the voiding dysfunction resulting from prostatic enlargement and bladder outlet obstruction [1, 2]. BPH can be histologically explains a proliferative process of both the stromal and epithelial elements of the prostate gland. BPH arises in the periurethral and transition zones of the prostate [3]. The prostatic enlargements perhaps elevate urination, involving frequent urination,

weak stream, or loss of urination control [4]. Aggravation of lower urinary tract symptoms can influence to chronic kidney problems, bladder stones, and urinary tract infections [5]. The severity of clinical BPH can be staged accordingly as stage I which means no significant obstruction and no bothersome symptoms; stage II which means no significant obstruction but has bothersome symptoms; stage III means significant obstruction regardless of symptoms; and stage IV means complications of clinical BPH such as retention of urine, recurrent haematuria, urinary tract infection, and bladder stones [6, 7].

Risk factors

BPH is a common and age-related disease as it is estimated that about 50% of men over the age of 50, and 80% of those older than 70 suffer from it [8]. BPH occurs in 30–40% of men in their fourth decade of life, and the occurrence of BPH elevates to 70–80% in men above 80 yrs of age [9]. High-fat diet is intrinsically correlated with BPH by stimulating inflammation and oxidative stress [10]. The risk factors of BPH involve metabolic syndrome, diabetes, obesity, hypertension, diet and sex hormone levels. Metabolic syndrome (metabolic syndrome involves hypertension, dyslipidaemia, glucose intolerance, central obesity and insulin resistance with compensatory hyperinsulinaem). Obesity is elevated levels of adipose tissue have been revealed to be associated with greater prostate volume [11-14].

Pathophysiology

The pathophysiology of bladder out let obstruction in men with BPH has been attributed to both static and dynamic factors. The static obstruction is owing to the bulk enlargement of the prostate gradually upon the prostatic urethra and bladder outlet, whereas the dynamic obstruction is related to the tension of prostate smooth muscle. Prostatic alpha1-adrenoceptors were more abundant than alpha2-adrenoceptors and were reported to directly mediate the tension of prostate smooth muscle [15-18]. The histopathology of BPH characteristically includes of a dual hyperplasia of the epithelial and stromal compartment of the transitional zone of the prostate. Epithelial hyperplastic features involve nodules composed of variably sized and sometimes cystically dilated prostatic glands with a retained basal cell layer, often exhibiting corpora amylacea and/or calcifications; stromal hyperplasia includes of nodular proliferation of bland-looking spindle cells with rounded to ovoid nuclei, commonly resembling smooth muscle cells. Several biological factors, involving oxidative stress, inflammation, androgens, and accelerated expression of multiple growth factors, have been associated with benign and malignant prostatic disorders [19-23]. Prostatic inflammation may be activated by bacterial or viral infections that initiate the generation of inflammatory cytokines and growth factors, resulting in the spontaneous growth of stromal and epithelial prostatic cells. Infection is correlated with the accelerated severity of BPH symptoms, and dysbiosis of urine microbiota is included in the pathogenesis of BPH [24, 25]. The T/DHT-androgen receptor complex within the nucleus of the prostate cells induces transcription of DNA and translation, with subsequent normal advancement, growth, and hyperplasia of the prostate. BPH develops due to an imbalance between growth and apoptosis (cellular death) in favor of growth, subsequently causing accelerate in cellular mass [26, 27]. The pathophysiological mechanisms of metabolic factors associated with BPH are not fully understood, but elevated sympathetic activity, pelvic ischemia, and systemic inflammation perhaps play crucial functions in BPH [28]. The nitric oxide–cyclic GMP (cGMP) pathway is another pathway included

in smooth muscle contractility. Phosphodiesterase type 5 (PDE5) negatively regulates smooth muscle contraction by hydrolysing cGMP (which is essential to muscle relaxation via its effects on intracellular calcium levels) [29, 30].

Diagnostic criteria

Prostate volume can be reliably measured using various imaging modalities involving ultrasonography, magnetic resonance imaging, and computerized tomography. Computerized tomography and magnetic resonance imaging are extremely costly procedures. Transrectal ultrasonography has become the standard for quantifying the level of prostate enlargement because the procedure can be performed in the outpatient setting [31, 32]. A digital rectal examination (DRE) is performed to assess both nodules suspicious for cancer and prostate size; currently, additional imaging studies have been recommended for patients considering surgical intervention [33]. A prostate-specific antigen (PSA) is generated by the prostate gland and is found to be abnormally enhanced in conditions such as prostate cancer, BPH, infection, or inflammation of the prostate [34].

Treatment

The medical therapies broadly used today for treatment of BPH are targeted to diminishing bladder outlet obstruction in order to decrease prostate volume and relax prostate smooth muscle tension [35]. The indications for treating BPH involve reversing existing signs and symptoms of the disease or inhibiting the progression of the disease [36]. Primary treatment options for BPH involve conservative management (watchful waiting and lifestyle modification) and use of medications (alpha blockers, 5- alpha reductase inhibitors and currently, phosphodiesterase inhibitors) [37].

Watchful waiting: Patients with mild symptoms (IPSS of ≤7) and no complicating factors or those with moderate symptoms and minimal bother can be managed with watchful waiting. Watchful waiting involves advice about lifestyle changes that can help to ameliorate or circumvent symptoms. These changes involve advice about volume, type and timing of liquids consumed, avoidance of caffeine (a diuretic), and abstinence of alcohol consumption in the evening and regulation of bowel movements with avoidance of constipation [38, 39].

Pharmacological treatment

The intention of medical therapy is to ameliorate symptoms, to mitigate BPH progression while ameliorating LUTS, lower the risk of progression and ameliorate QOL [40].

Alpha 1-blockers: Alpha-1 blockers are considered as the first-line treatment and are used in the availability of moderate-to-severe symptomatology. Terazosin and doxazosin are non-specific alpha-1 receptor blockers confirmed for hypertension, as well as BPH. Tamsulosin, alfuzosin, and silodosin have lower potential for orthostatic hypotension and syncope and this category of medications is considered an excellent choice due to the rapid onset of action. The mechanism of action of α1-blockers is to prevent the effect of norepinephrine released endogenously on smooth muscle cells of the prostate; thus, these

decreases the tone of the prostate, the consequent urethral obstruction and relax prostate smooth muscle tension and hormonal therapy preferentially decreases epithelial volume [41, 42]. When administering alpha-1 blocker for the treatment of LUTS/BPH the alpha-1 blocker choice should be depending on patient age and comorbidities and different adverse event profiles (eg, ejaculatory dysfunction, alters in blood pressure) [43].

5α-reductase inhibitors: The mechanism of action of 5α-reductase inhibitors category of medications is depending on the blockade of the enzyme 5α-reductase, which converts testosterone (T) into dihydrotestosterone (DHT), the hormone that mediates the effects of androgens on the prostate. Two 5α-RIs are available for clinical use: finasteride and dutasteride. The former selectively prevents 5α-reductase type 2, while the latter prevents both 5α-reductase type 1 and 2. 5α- RIs initiate apoptosis of prostate epithelial cells influencing to a reduction in prostate size by approximately 18–28% and reduce serum PSA levels by approximately 50% after six-twelve months of treatment. 5α-RI treatment should be recommended for patients with moderate-to-severe LUTS and enlarged prostate (>40 ml). Differently from α1-blockers, 5α- RI can inhibit prostate enlargement and the appearance of acute urinary retention [44, 45].

Muscarinic receptor antagonists: Muscarinic receptor antagonists act by blocking the muscarinic receptors present on smooth muscle cells, thereby decreasing irritative LUTS (urgency, frequency, or urge incontinence) and modulation of detrusor contractility; prevention of muscarinic receptors decreases smooth muscle tone and relieves symptoms. Muscarinic receptor antagonist's drugs elevate the volume of the bladder at the first contraction of the detrusor and the maximum cytometric capacity and reduce the contractility index of the bladder [45, 46]. Available agents involve non-selective antagonists, such as oxybutynin, and selective antagonists, such as solifenacin and tolterodine. Solifenacin is more selective for the muscarinic-3 receptor than the muscarinic-2 receptor. Tolterodine exhibits selectivity for the urinary bladder over salivary glands. For individuals who have a poor response to anti-muscarinic medicines or who have previously experienced adverse effects with these drugs, agonism of the β3-adrenoceptor might be an alternative treatment option [47, 48].

PDE5 inhibitors: PDE5 inhibitors they elevate the intracellular cyclic guanosine monophosphate, thus decreasing the regular muscle tone of the detrusor, prostate, and urethra and ameliorating blood perfusion and oxygenation in the lower urinary tract [49]. PDE5 prevention possibly accelerates tissue perfusion, modulates autonomic nervous system activity and prevents the prostatic inflammatory process, all of which lead to an improvement in voiding symptom. PDE5 inhibitor tadalafil is use to reduces detrusor pressure without profoundly changing Qmax [50, 51].

Transurethral microwave thermotherapy: Transurethral microwave thermotherapy (TUMT) uses microwave-induced heat to ablate prostatic tissue and is designed to have fewer major complications than TURP. Transurethral resection of the prostate (TURP), considered the "gold standard" treatment for patients with smaller prostate volumes (greater than 90 g). The patient is treated in an outpatient setting

under local anesthesia. The treatment catheter is then placed within the urethra, approved by the return of sterile water and transabdominal or transrectal ultrasound, and the balloon is inflated. The distal port contains the bladder balloon, permitting for urine drainage and cooling. A rectal probe perhaps inserted to monitor the rectal temperature [52-54].

CONCLUSION

Benign prostatic hyperplasia can be characterizes a proliferative process of both stomal and epithelial elements of the prostate. High-fat diet is intrinsically correlated with BPH by stimulating inflammation and oxidative stress. Prostatic alpha-1 adrenoceptors were more predominant than alpha-2 adrenoceptors and were reported to directly mediate the tension of prostate smooth muscle. Primary treatment options for BPH involve conservative management (watchful waiting and lifestyle modification) and use of medications (alpha blockers, 5- alpha reductase inhibitors, and, recently, phosphodiesterase inhibitors). Alpha blockers relax prostate smooth muscle tension and hormonal therapy preferentially decreases epithelial volume.

ABBREVIATIONS

BOO: Bladder outlet obstruction; BPH: Benign prostatic hyperplasia; DRE: Digital rectal examination; IPSS: International Prostate Symptom Score; LUTS: Lower urinary tract symptoms; PDE5: Phosphodiesterase type 5; PSA: Prostate-specific antigen; 5α RIs: 5α-reductase inhibitors; T/DHT: Testosterone into dihydrotestosterone; TUMT: Transurethral microwave thermotherapy; TURP: Transurethral resection of the prostate;

ACKNOWLEDGMENTS

The author would be grateful to anonymous reviewers for the comments that increase the quality of this manuscript.

Data Sources: Sources searched include Google Scholar, Research Gate, PubMed, NCBI, NDSS, PMID, PMCID, Scopus database, Scielo and Cochrane database. Search terms included: pathophysiology and management of benign prostatic hyperplasia

Funding

None

Competing interests

The author has no financial or proprietary interest in any of material discussed in this article.

REFERENCES

1. Russo, G.I.; Broggi, G.; Cocci, A.; Capogrosso, P.; Falcone, M.; Sokolakis, I.; Gül, M.; Caltabiano, R.; Di Mauro, M. Relationship between Dietary Patterns with Benign Prostatic Hyperplasia and Erectile Dysfunction: A Collaborative Review. Nutrients 2021, 13, 4148.

2. Russo, G.I.; Campisi, D.; Mauro, M.D.; Regis, F.; Reale, G.; Marranzano, M.; Ragusa, R.; Solinas, T.; Madonia, M.; Cimino, S.; et al. Dietary consumption of phenolic acids and prostate cancer: A case-control study in sicily, Southern Italy. Molecules 2017, 22, 2159.
3. Russo, G.I.; Di Mauro, M.; Regis, F.; Reale, G.; Campisi, D.; Marranzano, M.; Giudice, A.L.; Solinas, T.; Madonia, M.; Cimino, S.; et al. Association between dietary phytoestrogens intakes and prostate cancer risk in Sicily. Aging Male 2018, 21, 48–54.
4. Reale, G.; Russo, G.I.; Di Mauro, M.; Regis, F.; Campisi, D.; Giudice, A.L.; Marranzano, M.; Ragusa, R.; Castelli, T.; Cimino, S.; et al. Association between dietary flavonoids intake and prostate cancer risk: A case-control study in Sicily. Complement Ther. Med. 2018, 39, 14–18.
5. Russo, G.I.; di Mauro, M.; Cocci, A.; Cacciamani, G.; Cimino, S.; Serefoglu, E.C.; Albersen, M.; Capogrosso, P.; Fode, M.; Verze, P. Consulting "Dr Google" for sexual dysfunction: A contemporary worldwide trend analysis. Int. J. Impot. Res. 2019, 32, 455–461.
6. Salonia, A.; Bettocchi, C.; Boeri, L.; Capogrosso, P.; Carvalho, J.; Cilesiz, N.C.; Cocci, A.; Corona, G.; Dimitropoulos, K.; Gül, M.; et al. European Association of Urology Guidelines on Sexual and Reproductive Health—2021 Update: Male Sexual Dysfunction. Eur. Urol. 2021, 80, 333–357.
7. Kessler, A.; Sollie, S.; Challacombe, B.; Briggs, K.; Van Hemelrijck, M. The global prevalence of erectile dysfunction: A review. BJU Int. 2019, 124, 587–599.
8. Olabiyi, A.A.; Carvalho, F.B.; Bottari, N.B.; Lopes, T.F.; da Costa, P.; Stefanelo, N.; Morsch, V.M.; Akindahunsi, A.A.; Oboh, G.; Schetinger, M.R. Dietary supplementation of tiger nut alters biochemical parameters relevant to erectile function in L-NAME treated rats. Food Res. Int. 2018, 109, 358–367.
9. Olabiyi, A.A.; AlliSmith, Y.R.; Ukwenya, V.O. Quercetin enhances sexual behavior and improves ectonucleotidases activity in the hypothalamus of rats treated with cyclosporine. J. Food Biochem. 2021, 45, e13864.
10. Minhas, S.; Bettocchi, C.; Boeri, L.; Capogrosso, P.; Carvalho, J.; Cilesiz, N.C.; Cocci, A.; Corona, G.; Dimitropoulos, K.; Gül, M.; et al. European Association of Urology Guidelines on Male Sexual and Reproductive Health: 2021 Update on Male Infertility. Eur. Urol. 2021, 80, 603–620.
11. Lu, Y.; Kang, J.; Li, Z.; Wang, X.; Liu, K.; Zhou, K.; Wang, W.; Shen, C. The association between plant-based diet and erectile dysfunction in Chinese men. Basic Clin. Androl. 2021, 31, 1–10.
12. Trebaticky, B.; Muchova, J.; Ziaran, S.; Bujdak, P.; Breza, J.; Durackova, Z. Natural polyphenols improve erectile function and lipid profile in patients suffering from erectile dysfunction. Bratisl. Med. J. 2019, 120, 941–944.
13. Huetos, A.S.; Muralidharan, J.; Galiè, S.; Salas-Salvadó, J.; Bulló, M. Effect of nut consumption on erectile and sexual function in healthy males: A Secondary outcome analysis of the fertinuts randomized controlled trial. Nutrients 2019, 11, 1372.
14. Mykoniatis, I.; Grammatikopoulou, M.G.; Bouras, E.; Karampasi, E.; Tsionga, A.; Kogias, A.; Vakalopoulos, I.; Haidich, A.-B.; Chourdakis, M. Sexual Dysfunction Among Young Men: Overview of Dietary Components Associated with Erectile Dysfunction. J. Sex. Med. 2018, 15, 176–182.

15. Cassidy, A.; Franz, M.; Rimm, E.B. Dietary flavonoid intake and incidence of erectile dysfunction. Am. J. Clin. Nutr. 2016, 103, 534–541.
16. Bauer, S.R.; Breyer, B.N.; Stampfer, M.J.; Rimm, E.B.; Giovannucci, E.L.; Kenfield, S.A. Association of Diet with Erectile Dysfunction among Men in the Health Professionals Follow-up Study. JAMA Netw. Open 2020, 3, e2021701.
17. Broggi, G.; Lo Giudice, A.; Di Mauro, M.; Asmundo, M.G.; Pricoco, E.; Piombino, E.; Caltabiano, R.; Morgia, G.; Russo, G.I. SRSF-1 and microvessel density immunohistochemical analysis by semi-automated tissue microarray in prostate cancer patients with diabetes (DIAMOND study). Prostate 2021, 81, 882–892.
18. Broggi, G.; Lo Giudice, A.; Di Mauro, M.; Pricoco, E.; Piombino, E.; Ferro, M.; Caltabiano, R.; Morgia, G.; Russo, G.I. Insulin signaling, androgen receptor and PSMA immunohistochemical analysis by semi-automated tissue microarray in prostate cancer with diabetes (DIAMOND study). Transl. Res. 2021, 238, 25–35.
19. Li, Y.-Z.; Shi, B.-K.; Li, J.-Y.; Zhu, X.-W.; Liu, J.; Liu, Y.-L. Role of p-ERK1/2 in Benign Prostatic Hyperplasia during Hyperinsulinemia. Urol. J. 2020, 18, 225–229.
20. Kayode, O.T.; Owolabi, A.V.; Kayode, A.A.A. Biochemical and histomorphological changes in testosterone propionate-induced benign prostatic hyperplasia in male Wistar rats treated with ketogenic diet. Biomed. Pharmacother. 2020, 132, 110863.
21. Aljehani, A.A.; Albadr, N.A.; Nasrullah, M.Z.; Neamatallah, T.; Eid, B.G.; Abdel-Naim, A.B. Icariin ameliorates metabolic syndrome-induced benign prostatic hyperplasia in rats. Environ. Sci. Pollut. Res. 2021, 1–9.
22. Tsai, H.-H.; Chen, C.-W.; Yu, P.-L.; Lin, Y.-L.; Hsieh, R-H. Mangosteen pericarp components alleviate progression of prostatic hyperplasia and mitochondrial dysfunction in rats. Sci. Rep. 2020, 10, 322.
23. Russo, G.I.; Larganà, G.; Sebastianelli, A.; Cocci, A.; Mauro, M.; Di Rapallo, I.; Morgia, G.; Morgia, M.; La Vignera, S.; Condorelli, R.; et al. The Investigative Role of Statins in Ameliorating Lower Urinary Tract Symptoms (LUTS): A Systematic Review. J. Clin. Med. 2021, 10, 416.
24. Phua, T.J. The Etiology and Pathophysiology Genesis of Benign Prostatic Hyperplasia and Prostate Cancer: A New Perspective. Medicines 2021, 8, 30.
25. Kucera, R.; Pecen, L.; Topolcan, O.; Dahal, A.R.; Costigliola, V.; Giordano, F.A.; Golubnitschaja, O. Prostate cancer management: Long-term beliefs, epidemic developments in the early twenty-first century and 3PM dimensional solutions. EPMA J. 2020, 11, 399–418.
26. Olmedo-Requena, R.; Lozano-Lorca, M.; Salcedo-Bellido, I.; Jiménez-Pacheco, A.; Vázquez-Alonso, F.; García-Caballos, M.; Sánchez, M.-J.; Jiménez-Moleón, J.-J. Compliance with the 2018 World Cancer Research Fund/American Institute for Cancer Research Cancer Prevention Recommendations and Prostate Cancer. Nutrients 2020, 12, 768.
27. Vickman, R.E.; Franco, O.E.; Moline, D.C.; Vander Griend, D.J.; Thumbikat, P.; Hayward, S.W. The role of the androgen receptor in prostate development and benign prostatic hyperplasia:A review. Asian J. Urol. 2020, 7, 191–202.

28. Kuo, Y.-J.; Sung, F.-C.; Hsieh, P.-F.; Chang, H.-P.; Wu, K.-L.; Wu, H.-C. Metformin reduces prostate cancer risk among men with benign prostatic hyperplasia: A nationwide population-based cohort study. Cancer Med. 2019, 8, 2514–2523.
29. Da Silva, M.H.A.; De Souza, D.B. Current evidence for the involvement of sex steroid receptors and sex hormones in benign prostatic hyperplasia. Res. Rep. Urol. 2019, 11, 1–8.
30. Kensler, K.H.; Rebbeck, T.R. Cancer Progress and Priorities: Prostate Cancer. Am. Assoc. Cancer Res. 2020, 29, 267–277.
31. Sinha, A.; Huang, V.; Livingstone, J.; Wang, J.; Fox, N.S.; Kurganovs, N.; Ignatchenko, V.; Fritsch, K.; Donmez, N.; Heisler, L.E.; et al. The Proteogenomic Landscape of Curable Prostate Cancer. Cancer Cell 2019, 35, 414–427.
32. Charmpi, K.; Guo, T.; Zhong, Q.; Wagner, U.; Sun, R.; Toussaint, N.C.; Fritz, C.E.; Yuan, C.; Chen, H.; Rupp, N.J.; et al. Convergent network effects along the axis of gene expression during prostate cancer progression. Genome Biol. 2020, 21, 302.
33. Liss, M.A.; Leach, R.J.; Sanda, M.G.; Semmes, O.J. Prostate Cancer Biomarker Development: National Cancer Institute's Early Detection Research Network Prostate Cancer Collaborative Group Review. Am. Assoc. Cancer Res. 2020, 29, 2454–2462.
34. Jin Cho, W.; Pyo, J.S. Immunohistochemical analysis of the impact of ischemic change in benign prostatic hyperplasia. Pathol. Res. Pract. 2020, 216, 152694.
35. Ungvari, Z.; Tarantini, S.; Donato, A.J.; Galvan, V.; Csiszar, A. Mechanisms of vascular aging. Circ. Res. 2018, 123, 849–867.
36. Marchio, P.; Guerra-Ojeda, S.; Vila, J.M.; Aldasoro, M.; Victor, V.M.; Mauricio, M.D. Targeting early atherosclerosis: A focus on oxidative stress and inflammation. Oxid. Med. Cell. Longev. 2019, 2019, 1–32.
37. Donato, A.J.; Machin, D.R.; Lesniewski, L.A. Mechanisms of dysfunction in the aging vasculature and role in age-related disease. Circ. Res. 2018, 123, 825–848.
38. Rizzuti, A.; Stocker, G.; Santos, H.O. Exploring the Role of Testosterone Replacement Therapy in Benign Prostatic Hyperplasia and Prostate Cancer: A Review of Safety. Uro 2022, 2, 30–39.
39. Byun, S.-H.; Min, C.; Bang, W.; Yang, B.-E.; Hong, S.J.; Park, S.C.; Choi, H.G. A Cross-Sectional Study for Association between Periodontitis and Benign Prostatic Hyperplasia Using the Korean Genome and Epidemiology Study Data. Coatings 2022, 12, 265.
40. Byun, S.H.; Lee, S.; Kang, S.H.; Choi, H.G.; Hong, S.J. Cross-Sectional Analysis of the Association between Periodontitis and Cardiovascular Disease Using the Korean Genome and Epidemiology Study Data. Int. J. Environ. Res. Public Health 2020, 17, 5237.
41. Byun, S.H.; Min, C.; Hong, S.J.; Choi, H.G.; Koh, D.H. Analysis of the Relation between Periodontitis and Chronic Gastritis/Peptic Ulcer: A Cross-Sectional Study Using KoGES HEXA Data. Int. J. Environ. Res. Public Health 2020, 17, 4387.
42. Cardoso, E.M.; Reis, C.; Manzanares-Cespedes, M.C. Chronic periodontitis, inflammatory cytokines, and interrelationship with other chronic diseases. Postgrad. Med. 2018, 130, 98–104.

43. Fang, C.; Wu, L.; Zhao, M.J.; Deng, T.; Gu, J.M.; Guo, X.P.; Li, C.; Li, W.; Zeng, X.T. Periodontitis Exacerbates Benign Prostatic Hyperplasia through Regulation of Oxidative Stress and Inflammation. Oxid. Med. Cell. Longev. 2021, 2021, 2094665.
44. Cakir, S.S.; Polat, E.C.; Ozcan, L.; Besiroglu, H.; Otunctemur, A.; Ozbek, E. The effect of prostatic inflammation on clinical outcomes in patients with benign prostate hyperplasia. Prostate Int. 2018, 6, 71–74.
45. : Ratajczak, W.; Lubkowski, M.; Lubkowska, A. Heat Shock Proteins in Benign Prostatic Hyperplasia and Prostate Cancer. Int. J. Mol. Sci. 2022, 23, 897.
46. Franco A et al. Transurethral Microwave Thermotherapy for Benign Prostatic Hyperplasia: An Updated Cochrane Review. World J Mens Health 2022 Jan 40(1): 127-138.
47. Foo TK. What is a disease? What is the disease clinical benign prostatic hyperplasia (BPH)? World Journal of Urology (2019) 37:1293–1296.
48. Launer BM. Et al. The rising worldwide impact of benign prostatic hyperplasia. BJU Int. 2021 June; 127(6): 722–728.
49. Feinsten L, Matlaga B. Urologic Diseases in America. US Department of Health and Human Services. Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2018:97–160.
50. Welliver C, Feinstein L, Ward JB et al. Trends in lower urinary tract symptoms associated with benign prostatic hyperplasia, 2004 to 2013: the Urologic Diseases in America Project. J Urol 2020; 203: 171–8.
51. Fitzmaurice C, Akinyemiju TF, Al Lami FH et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the global burden of disease study. JAMA Oncol 2018; 4: 1553–68.
52. Madersbacher S et al. Pathophysiology of Benign Prostatic Hyperplasia and Benign Prostatic Enlargement: A Mini-Review. Gerontology 2019; 65:458–464.
53. Xiong Y et al. The association between metabolic syndrome and lower urinary tract symptoms suggestive of benign prostatic hyperplasia in aging males: evidence based on propensity score matching. Transl Androl Urol 2021;10(1):384-396.
54. Franco JVA, Jung JH, Imamura M, Borofsky M, Omar MI, Escobar Liquitay CM, Young S, Veroniki AA, Garegnani L, Dahm P. Minimally invasive treatments for lower urinary tract symptoms in men with benign prostatic hyperplasia: a network meta-analysis (Protocol). Cochrane Database of Systematic Reviews 2020, Issue 6. Art. No.: CD013656.