



Is COVID-19 a risk factor for progression of benign prostatic hyperplasia and exacerbation of its related symptoms?: a systematic review

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Abstract

Background To explore the potential mechanisms of SARS-CoV-2 in targeting the prostate gland, leading to exacerbation of benign prostatic hyperplasia (BPH) symptoms and greater risks of BPH complications such as acute urinary retention.

Methods A categorized and comprehensive search in the literature has been conducted by 10 April 2021 using international databases including PubMed, Embase, Web of Science, Scopus, and Cochrane Library in line with the PRISMA guidelines recommendations. PICO strategy was used to formulate the research question. The following terms were used: urology, COVID-19, coronavirus, BPH, inflammation, androgen receptors, LUTS, IPSS, PSA, and SARS-CoV-2 or a combination of them. Studies with irrelevant purposes and duplicates were excluded. The selected studies were performed on humans and published in English.

Results The research revealed 89 articles. After title screening and considering exclusion criteria, 52 papers were included for the systematic review. BPH is a common condition affecting older men. SARS-CoV-2 infects the host cell by binding to angiotensin converting enzyme 2 (ACE2). A hyperactivated RAS system during infection with SARS-CoV-2 may lead to activation of pro-inflammatory pathways and increased cytokine release. Thus, this virus can lead to exacerbation of lower urinary tract symptoms (LUTS) and trigger inflammatory processes in the prostate gland. Since androgen receptors (AR) play an important role in the BPH pathophysiology and infection with SARS-CoV-2 may be androgen-mediated, BPH progression and its related symptoms can be a complication of COVID-19 through AR involvement and metabolic disturbances.

Conclusions Based on the current findings, SARS-CoV-2 can possibly damage the prostate and worsen BPH and its related LUTS through ACE2 signaling, AR-related mechanisms, inflammation, and metabolic derangement. We encourage future studies to investigate the possible role of COVID-19 in the progression of BPH-related LUTS and examine the prostatic status in susceptible patients with relevant available questionnaires (e.g., IPSS) and serum biomarkers (e.g., PSA).

Introduction

The outbreak of the ongoing global Coronavirus disease 2019 (COVID-19) pandemic that was caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in late 2019 in Wuhan, China; since then, the world has faced a great global catastrophe; this life-threatening crisis has proven challenging to overcome [1]. The most common manifestation of the novel coronavirus seems to be pneumonia [2]; however, it is now widely accepted that the virus can present with symptoms outside the respiratory tract including digestive tract symptoms such as nausea, vomiting, and diarrhea [3]. Angiotensin-converting enzyme 2 (ACE2) appears to be a

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receptor for SARS-CoV-2, to which the virus binds to, enters, and infects the host cell [4]. Moreover, recent studies have found that co-expression of ACE2 and TMPRSS2 in an organ is crucial for the virus to be able to infect the organ [5]. Previously, it was believed that the virus mainly infected the lungs although discovering the co-expression of ACE2 and TMPRSS2 in other organs such as the kidneys, testes, and prostate raises the question of whether or not the virus can affect the aforementioned organs [6].

Benign prostatic hyperplasia (BPH) is a histologic diagnosis defined as excessive growth of the epithelial and stromal cells located in the transition zone of the prostate gland. BPH is the most common cause of benign prostatic enlargement (BPE), benign prostatic obstruction, and bladder outlet obstruction in older men [7–9]. Lower urinary tract symptoms (LUTS) are considered a consequence of a wide range of etiologies such as BPH and non-prostatic conditions including dysfunction of the bladder [10, 11]. Furthermore, international prostate symptom score (IPSS), as a validated questionnaire, and serum prostate-specific antigen (PSA) measurement are considered to evaluate the patients with BPH [10, 12].

There are different risk factors related to the development of BPH such as LUTS, prostate growth, old age, sex-related hormones, and chronic inflammation [13]. The prevalence of BPH is increased in an age-dependent manner. It is estimated that 8% and 50% of male population at the 4th and 6th decade of life, respectively, are diagnosed with pathological BPH [14].

Recent studies have shown that males are more susceptible to SARS-CoV-2 infection and elder population seems to develop more severe cases of COVID-19 and subsequently they are more susceptible to hospitalization [15, 16]. Furthermore, a significant number of patients with COVID-19 are asymptomatic carriers [17, 18]. As mentioned before, BPH increases in an age-dependent manner and then, a considerable number of older males are diagnosed with BPE [14]. Thus, one can hypothesize that a remarkable group of older male patients with COVID-19 including severe cases may have BPH as a comorbid condition and this condition may be exacerbated by COVID-19. Recently, emerging studies have proposed that LUTS may be increased early symptoms of COVID-19 and IPSS, especially in older males, may be possible complications of this disease [19, 20]. To date, no study has investigated the potential mechanisms of SARS-CoV-2 in causing BPH-related complications, LUTS or exacerbation of a previously diagnosed BPE in severe cases, and asymptomatic carriers of COVID-19 and the underlying mechanisms resulting in this condition as a complication of COVID-19 are not elucidated.

In this review, the main purpose was to explore the potential mechanisms of SARS-CoV-2 in targeting the

prostate gland, leading to progression of BPH, or exacerbation of its related LUTS.

Materials and methods

Search strategy and selection criteria

A categorized and comprehensive search in the literature was conducted by 10 April 2021 using international databases including PubMed, Embase, Web of Science, Scopus, and Cochrane Library in line with the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines [21]. All the records in English were included for investigating their eligibility, both published and peer-reviewed on-line publications. Additional sources were identified from citations of the retrieved literature. There was no limitation on sample size. Published reports of experiences with the SARS-CoV-2 have increased greatly in the past months, but no randomized trials to date regarding possible treatments have been identified regarding possible treatments. Most reports related to BPH or male prostate problems involved small cohorts, case reports, and editorials. Similarly, prior publications of other coronaviruses were limited in number. We reviewed all the titles for considering their eligibility. Full-text articles were then reviewed and evaluated for inclusion by authorship teams. The authors acknowledge that the number of publications about the novel SARS-CoV-2 is increasing at an exponential rate and there may be bias toward reporting of positive findings. We used a broad inclusive search strategy in order to prevent missing any relevant records. Two experienced investigators conducted the systematic search. Population, intervention, comparison, and outcome strategy was used to formulate the research question: “Are BPH patients infected with SARS-CoV-2 at greater risk of developing LUTS and BPH-related complications compared to the normal population?” (Table 1). The following phrases were searched in different databases: “severe acute respiratory syndrome coronavirus 2,” “2019 nCoV,” “SARS-CoV-2,” “coronavirus,” “COVID-19,” “benign prostatic hyperplasia,” “inflammation,” “androgen

Table 1 PICO strategy was used to formulate the research question: “Are BPH patients infected with SARS-CoV-2 at greater risk of developing LUTS and BPH-related complications compared to the normal population?”.

P (Population)	Patients with BPH
I (Intervention or exposure)	Infection with SARS-CoV-2
C (Comparison)	Normal population
O (Outcome)	Lower urinary tract symptoms (LUTS) and BPH-related complications

receptors,” “lower urinary tract symptoms,” “bladder outlet obstruction,” “benign prostatic enlargement,” “international prostate symptom score,” “prostate specific antigen,” “cytokine storm,” “angiotensin-converting enzyme 2 receptor,” “ACE2,” “5- α reductase inhibitor,” and “prostate involvement” or a combination of them in the titles/abstracts.

Data extraction

Two authors (AH and FM) independently screened for inclusion, using the pre-specified criteria. If it was clear from the abstract that the study did not meet the selection criteria through reviewing the abstract, it was excluded. If it was unclear, the full paper was retrieved. Then, for relevant records, the full text was evaluated; discrepancies were resolved via consensus after discussion between two of the authors.

The search revealed 89 manuscripts after removal of duplicates and inappropriate articles. Fifty-five manuscripts were related to prostate gland and coronaviruses. Small cohorts, case reports, comments on guidelines, guidelines, editorials were retrieved. After exclusion, 52 manuscripts were included in the review based on relevance and new data.

The PRISMA flow chart demonstrating the process for the systematic search of the literature and selection of the studies is shown in Fig. 1. Furthermore, Table 2 showed

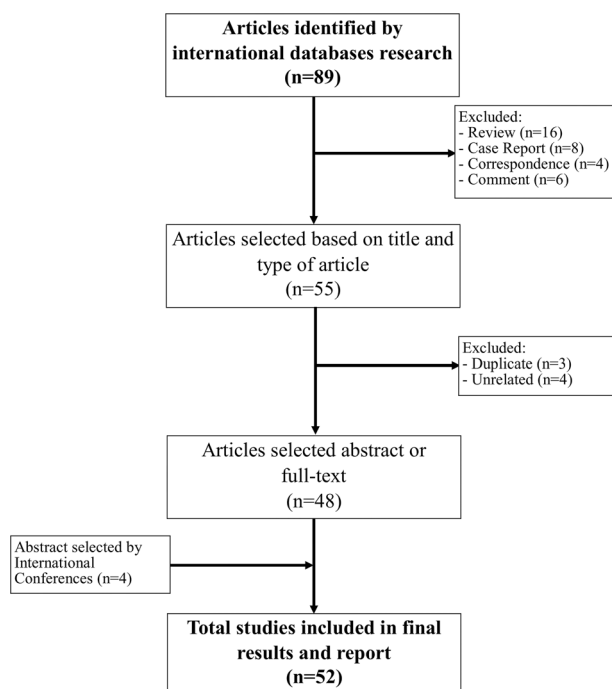


Fig. 1 Article’s selection process: the PRISMA flow chart. Literature search according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.

grouping of the relevant studies about mechanisms of progression of BPH as a consequence of SARS-CoV-2 infection.

Results

Potential mechanism of SARS-CoV-2 infection in the BPH progression through RAS dysregulation

The renin–angiotensin system (RAS) is a hormonal cascade that regulates the blood pressure and cardiovascular function through its components including angiotensin-II (Ang-II), and angiotensin converting enzyme (ACE) and RAS hyperactivity is associated with hypertension [22, 23]. Augmented Ang-II level is associated with cellular growth and its activity is mainly mediated by angiotensin-II type 1 receptor (AT1R) [24].

It is well-established that RAS components are locally present in the prostate gland [24, 25]. Ang-II has been detected in epithelial basal layer of the prostate and AT1R was found in the smooth muscle cells of both vessels and the stroma of the prostate gland in some studies [25, 26]. There is evidence that the expression of ACE and Ang-II was markedly increased in patients with BPH. Moreover, AT1R expression is downregulated in patients with BPH due to increased level of Ang-II [26]. Thus, this highlights the potential role of RAS in the development of BPH, and RAS blockade can be suggested as a therapeutic option in patients with BPH.

ACE2 is an enzyme that is known to counterbalance the effects of ACE by cleaving Ang-II to Ang (1–7), a product that binds to Mas receptor. Studies have demonstrated that ACE2 has anti-fibrotic and anti-inflammatory activities and acts as a vasodilator [27–30]. As mentioned before, Ang-II is remarkably increased in BPH and it has been revealed that Ang-II leads to downregulation of ACE2 and subsequently, a decrease in Ang (1–7) will be observed [26]. Given that Ang-II leads to cellular growth and ACE2-Ang-(1–7)/Mas receptor pathway counterbalances ACE and Ang-II functions, the potential role of ACE2 as a novel therapeutic option for treating BPH [31] is emphasized (Fig. 2).

Studies on SARS-CoV-2 characteristics have delineated that the virus binds to ACE2 receptor, which is expressed in many human tissues such as lung, kidney, prostate, and pancreas, and infects the target tissue. Thus, there is mounting concern about the possibility of the mentioned organs involvement as targets of SARS-CoV-2 [6]. It has been demonstrated that serine protease TMPRSS2 is necessary for priming the viral spike protein and the co-expression of TMPRSS2 and ACE2 is crucial for cell entry. Moreover, it has been suggested that when

Table 2 Grouping the relevant studies about mechanisms of progression of BPH as a consequence of SARS-CoV-2 infection.

Subheadings of the results	Main finding	Year	References
RAS dysregulation studies	<p>The main host cell receptor for the viral entry of SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2). Analysis of RNA-seq profiling data of 27 organ types (including prostate) verified the ACE2 expression in the epithelial cells.</p> <p>Hyperactivation of the renin-angiotensin aldosterone system (RAAS) results in the augmentation of the bioactive peptide hormone angiotensin-II, which downregulates the ACE2-angiotensin 1-7/Mas receptor pathway and upregulates angiotensin receptor type 1-mediated signaling, and finally may lead to proliferation of cellular elements in the prostatic tissue. ACE2, Ang-(1-7), and the Mas receptor can be employed as a novel target of treatment in BPH/LUTS.</p> <p>The presence of Ang-II peptide in the basal layer of the epithelium and AT(1) receptors on stromal smooth muscle, suggests that Ang-II may mediate paracrine functions on cellular growth and smooth muscle tone in the prostatic tissue. AT(1) receptor downregulation in BPH may be induced by hyperstimulation of the receptor secondary to a rise in the local levels of Ang-II in BPH.</p> <p>The prevailing presence of AT(1) receptors in the periurethral region of the prostatic tissue suggests a potential role for Ang-II in modulating smooth muscle cell tone, cellular growth, and possibly micturition. This can suggest a key role for Ang-II in modulating the sympathetic transmission in prostate.</p> <p>A localized concentration of angiotensin converting enzyme (ACE) is observed in the glandular epithelium of prostatic tissue and an abnormal increase in its expression at protein and mRNA level is seen in BPH.</p> <p>COVID-19-induced cytokine storm increases the activity of the RAAS and complement system.</p> <p>Viral or bacterial infections may induce local inflammation characterized by proliferation in inflammatory cytokines, chemokines, and growth factors. Epithelial and stromal cell growth of the prostate is triggered by this inflammatory response.</p> <p>There is a strong correlation between acute and chronic inflammation seen in prostatic enlargement and LUTS, which can be a primary reason of prostatic fibrosis and hence, bladder outlet obstruction (BOO).</p> <p>Expression of androgen receptor variant 7 (AR-V7) secondary to nuclear factor-kappa B (NF-κB) activation in the prostatic tissue is linked with increased severity of BPH.</p> <p>Inflammation in the prostate seems to be a major risk factor for prostatic growth and exacerbation of the related symptoms. Stromal-derived IL-8 is a possible candidate in the link between chronic inflammation and proliferation in stromal cells.</p> <p>Inflammatory cytokines IL-6, IL-8, and IL-17 are responsible for induction of fibromuscular growth through inducing COX-2 expression or an autocrine or paracrine loop. Toll-like receptor signaling triggers the immune response, which is mediated predominantly by macrophages and T cells. Conversely, anti-inflammatory markers including macrophage inhibitory cytokine-1 are diminished in symptomatic BPH tissues.</p> <p>All BPH-derived specimens showed a rise in CD45+ leukocytes such as CD3+ T lymphocytes, CD11c+ macrophages and CD20+ B lymphocytes when compared to normal prostate.</p> <p>Transmembrane protease, serine 2 (TMPRSS2), which is a serine protease essential for priming of the viral spike protein, requires androgen receptor activity for its gene transcription.</p> <p>Androgenic alopecia is a common finding in a remarkable portion of the male patients hospitalized due to COVID-19.</p> <p>Alteration in AR signaling pathway in stromal and epithelial cells of the prostatic tissue is considered a major underlying cause for chronic inflammation and BPH development.</p>	2020	Xu et al. [6]
		2018	Singh et al. [31]
		2002	Dinh et al. [26]
		2001	Dinh et al. [24]
		2001	Nassis et al. [25]
		2020	Mahmudpour et al. [41]
		2019	Madersbacher et al. [13]
		2016	Bushman et al. [38]
		2016	Austin et al. [39]
		2011	Chughtai et al. [32]
		2006	Kramer et al. [34]
		1992	Theyer et al. [35]
		2020	Wambier et al. [51]
		2020	Wambier et al. [52]
		2019	Vickman et al. [71]
Inflammation-related studies			
Androgen related studies			

Table 2 (continued)

Subheadings of the results	Main finding	Year	References
	Infiltration of macrophages potentiates the proliferation of stromal cells through androgen receptor (AR)-signaling pathway, although transitional and peripheral zones of the prostate appear to respond differently due to variable responses to AR signaling in the mentioned zones.	2017	Xu et al. [50]
	A drop in the expression of AR in luminal cells of patients with BPH correlates with a higher degree of regional prostatic inflammation.	2016	Zhang et al. [48]
	Proliferation of epithelial cells leads to the growth of the stromal cells via epithelial–stromal cell interaction and epithelial–mesenchymal transition (EMT). Overall, AR signaling is responsible for infiltrating macrophages and epithelial and stromal cell proliferation and consequently development of BPH.	2013	Izumi et al. [43]
	Androgen receptor (AR)/inflammatory cytokine CCL3-dependent pathway is an important underlying mechanism in the infiltration of macrophages and subsequently stromal cell proliferation in the prostate.	2012	Wang et al. [49]
	TGF- β seems to be the main marker in EMT and BPH is characterized by promoted growth of mesenchymal-like cells in prostatic epithelium and endothelium.	2009	Alonso-Magdalena et al. [45]
	High levels of dehydrotestosterone (DHT) are associated with pathologic prostate growth in the adult prostate tissue.	2003	Carson III et al. [55]
	5- α reductase inhibitors (5-ARIs) may impair the ability of the lungs in regeneration and may be associated with worse outcomes in COVID-19.	2020	Adamowicz et al. [54]
	Taking 5-ARIs, which are prescribed in androgenetic alopecia and benign prostatic hyperplasia, is associated with decreased symptoms and severity of COVID-19.	2020	McCoy et al. [56]
	Finasteride, which is a single receptor 5-alpha reductase inhibitor (5-ARI), acts by blocking dihydrotestosterone (DHT). Dutasteride, a dual receptor DHT blocker, has a higher potency than its predecessor, finasteride.	2020	Dhurat et al. [72]
	Finasteride treatment can augment estradiol levels and also block posttraumatic cytokine secretion of alveolar macrophages (AM), as well as decrease concentration of MCP-1 and MIP-1 β in lung tissue.	2011	Zeckey et al. [59]
	Finasteride administration prevents the increase in cytokine plasma levels, decreases DHT, and increases 17beta-estradiol plasma concentrations. Neutrophil infiltration and edema formation in the lung are also reduced by finasteride.	2007	Frink et al. [58]
	Finasteride, a selective inhibitor of the type 2 isoenzyme, can cause a significant drop in serum DHT level, although dutasteride by inhibiting both isoenzymes can decrease DHT levels more significantly.	2004	Clark et al. [57]
Metabolic derangement related studies	Since ACE2 is expressed in metabolic tissues such as pancreatic beta cells, adipose tissue, the small intestine, and the kidneys, it is plausible that SARS-CoV-2 may deteriorate pre-existing metabolic abnormalities or even lead to new onset ones.	2020	Rubino et al. [65]
	Pre-existing cardiovascular disease seems to be linked with worse outcomes and increased risk of death in patients with COVID-19, whereas COVID-19 itself can also induce myocardial injury, arrhythmia, acute coronary syndrome, and venous thromboembolism.	2020	Nishiga et al. [66]
	The localization of ACE2 expression in the endocrine part of the pancreas suggests that SARS coronavirus enters and damages islets causing acute diabetes.	2010	Yang et al. [64]
	Metabolic syndrome (MetS), defined as a set of metabolic abnormalities such as high visceral adiposity and insulin resistance, appear to be a common condition in patients with BPH and LUTS and probable underlying mechanisms leading to BPH are sex-related hormonal change, systemic inflammation, insulin resistance, and aberrant lipid profile.	2017	Ngai et al. [63]
	Diabetes-induced hyperglycemia and the subsequent insulin resistance is related to the increased risk of BPH and LUTS.	2014	Breyer et al. [60]

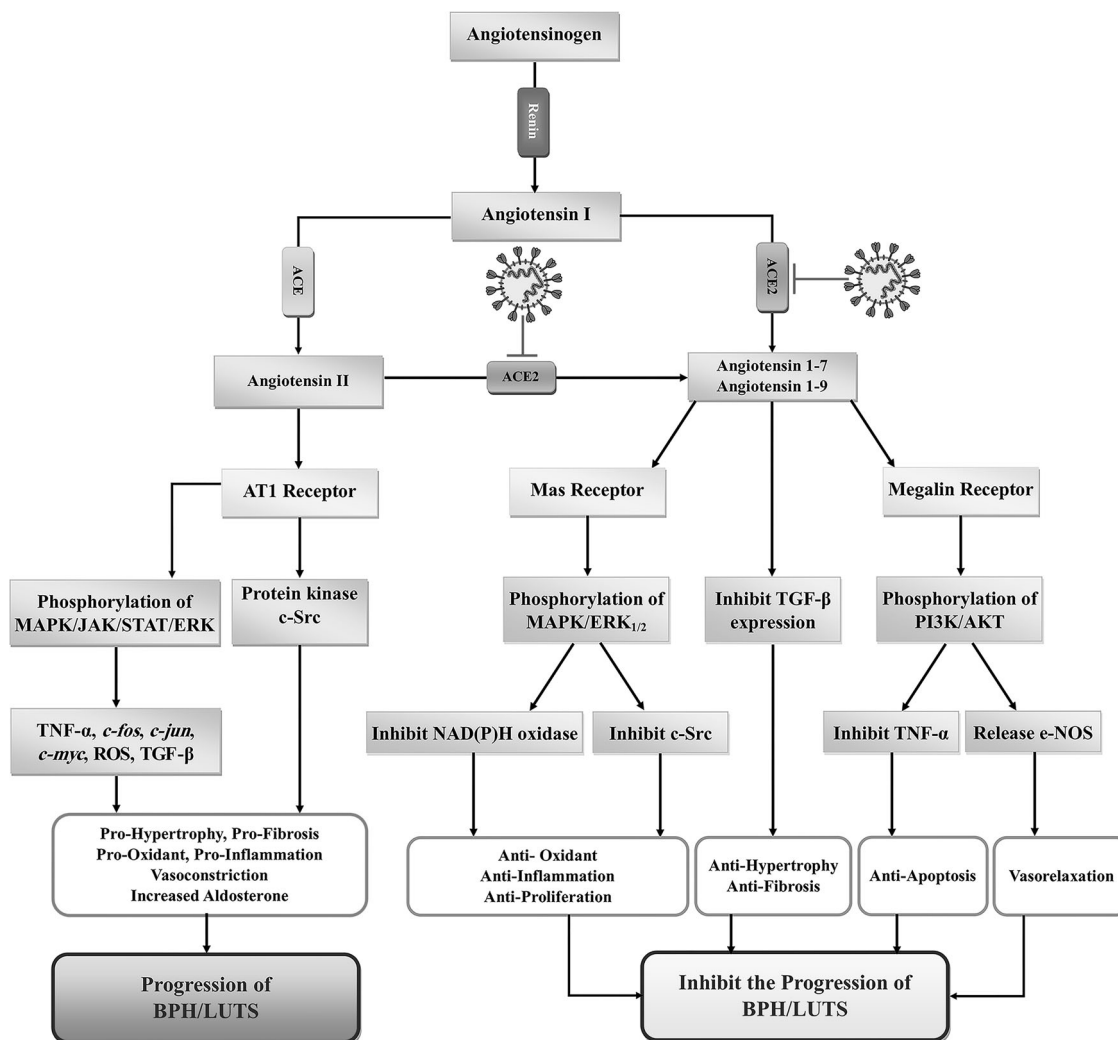


Fig. 2 The role of the ACE2 and the detrimental effect of SARS-CoV-2 in the RAAS during progression of BPH/LUTS. Renin cleaves angiotensinogen into angiotensin I (Ang I), and the circulating Ang I is hydrolyzed to Ang-II by ACE. Ang-II activates the AT1R to lead to pro-hypertrophy, pro-fibrosis, pro-oxidant, pro-inflammation, vasoconstrictor response, and to increase aldosterone synthesis. ACE2 directly hydrolyzes Ang I and Ang-II to generate Ang 1-9 and Ang 1-7, respectively. Ang 1-7 binds to the Mas R/megalin R, which leads

to the cellular signaling that opposes the Ang-II effects on BPH progression and does not stimulate aldosterone secretion. The SARS-CoV-2 disturbs the balance of RAAS by downregulating the ACE2 expression levels. Conclusively, the disproportion between AT1R and Mas R/megalin R axes in infected patients with SARS-CoV-2 contributes to the development of BPH/LUTS and more severe inflammatory reactions.

the virus binds to ACE2 receptor through its spike protein, it leads to downregulation of ACE2 [4]. Given the fact that ACE2, which is a component of ACE2/Ang-(1-7)/Mas system, counteracts the proliferative and inflammatory effects of Ang-II by controlling and inhibiting infection and inflammation it can be concluded that infection with SARS-CoV-2 and a subsequent downregulation of ACE2 can lead to aggravation of a previously diagnosed BPE. Therefore, diminished ACE2 expression and following ACE2 loss of function in the cellular membranes of the prostate tissue, due to viral invasion, can be trigger signals for progression of BPH (Fig. 2). Consequently, this highlights the urgent need for

future studies to investigate the possibility of BPH progression as a result of COVID-19.

The possible role of inflammation in the progression of BPH symptoms secondary to SARS-CoV-2 infection

A correlation between the development of BPH and chronic inflammation has been assumed. This inflammation can be triggered by etiologies such as bacterial or viral infection [13, 32]. First, bacterial or viral infection can lead to localized prostatic inflammation and subsequently production of different inflammatory cytokines such as IL-6, IL-8, IL10,

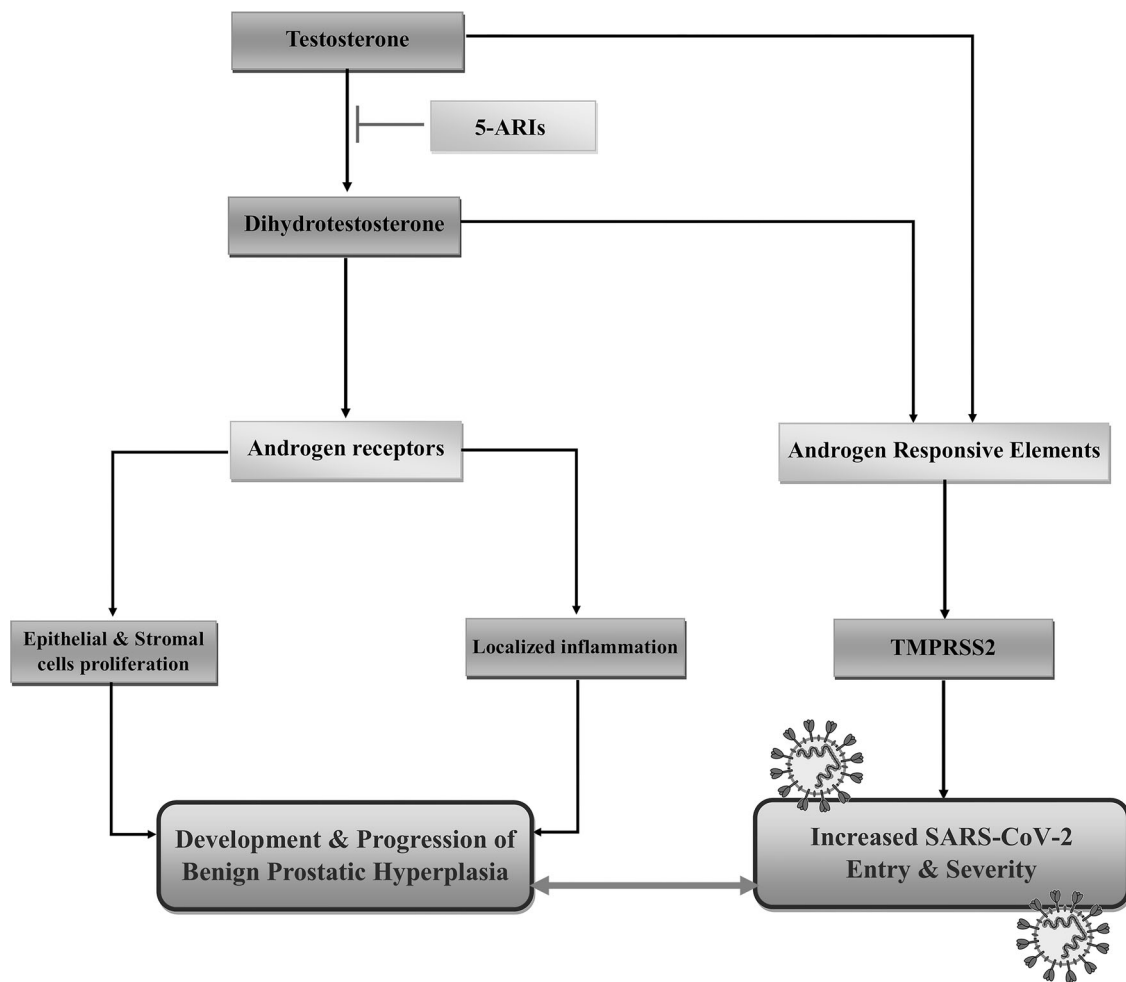


Fig. 3 The story of androgens and androgen receptors (AR) in the development of BPH and severity of COVID-19. There are bidirectional interactions between BPH and COVID-19. Increased production of dihydrotestosterone (DHT) and AR activity through promoting growth in the prostate epithelial and stromal cells and triggering a localized inflammation led to the development and progression of BPH. TMPRSS2, which is an essential serine protease for priming of the spike protein of SARS-CoV-2, requires AR activity and

androgen-responsive elements for its gene transcription. 5-alpha reductase inhibitors (5-ARIs) increase androgen levels and possibly the severity of COVID-19 via inhibiting the conversion of testosterone to dihydrotestosterone. On the other hand, these inhibitors probably reduce the complications of COVID-19 by reducing DHT production, increasing estradiol levels, and suppressing some inflammatory mechanisms.

and TNF- β by stromal prostatic cells and infiltrated lymphocytes and macrophages [13, 33–35]. Moreover, it has been demonstrated that the inflammatory process in the prostate can result in the release of self-antigens, trigger an autoimmune response, and subsequently cause tissue damage [36].

It has been suggested that prostatic inflammation is a risk factor for BPH progression [13]. A study has demonstrated that stromal nodules containing a remarkable number of B- and T-cell lymphocytes were detected in specimens from patients with BPH, whereas these nodules were not detected in normal prostates [37]. Theyer et al. investigated the characterization of the leukocytes in BPH and found a significant increase in CD45⁺ leukocytes including macrophages, B-cell, and T-cell lymphocytes were mainly present

in the interstitium [35]. Furthermore, inflammatory mediators seem to play a major role in the progression and severity of BPH and LUTS [38]. There is evidence that nuclear factor-kappa B (NF- κ B) pathway is activated in BPH patients and is closely associated with the disease severity [39]. Notably, systemic inflammation may contribute to LUTS-related irritative symptoms especially in overweight males [40]. As a result, accumulating evidence suggests the potential role of inflammatory mediators and infiltrated inflammatory cells in BPH progression and severity.

Studies have revealed that ACE2 and its product Ang (1–7) seem to function as an antiproliferative and anti-inflammatory agent and modulate leukocyte infiltration and cytokine secretion by counterbalancing the Ang-II effects

[41]. Moreover, Ang (1–7) seems to have anti-inflammatory effects through suppressing the NF- κ B pathway and cytokines such as IL-6, tumor necrosis factor (TNF)- α , and IL-8 [41, 42]. SARS-CoV-2 induces the suppression of ACE2 in order to gain entry to the target cells [4]. These results provide evidence that infection with SARS-CoV-2 and subsequently suppression of ACE2 may lead to activation of pro-inflammatory pathways, increased cytokine release, and consequently cause inflammatory responses in vulnerable organs such as the prostate. Although the inflammatory mechanism in progression of BPH and its symptoms is still obscure and needs to be elucidated, it can be hypothesized that SARS-CoV-2 can lead to development of irritative symptoms of BPH and trigger inflammatory process in the prostate gland, so prospective studies can help to clarify this issue.

Evidence for the role of androgen receptors in BPH development as a consequence of SARS-CoV-2 infection

The theory that androgen receptors (AR) play a key role in the development of BPH is well-established [43]. AR are widely expressed in both epithelial and stromal cells of the prostate. First, studies have revealed that AR result in promoting growth in the prostate epithelial cells [44]. Although it has been demonstrated that BPH consists of more stromal cells rather than epithelial cells, proliferation of epithelial cells lead to the growth of the stromal cells via epithelial–stromal cell interaction and epithelial–mesenchymal transition [45]. While there is no definite solidarity regarding any alteration in AR expression throughout BPH progression, a rise in stromal to epithelial AR ratio is noted in BPH that plays a key role in the progression of BPH [46]. Next, accumulating evidence suggests that AR induce stromal cell proliferation and consequently lead to development of BPH. AR play a role in increased recruitment of migrating macrophages into the prostate stromal cells; therefore, they cause promotion of stromal cell proliferation and subsequently lead to BPH progression [43]. Contemporary data has assumed that modified AR expression can also contribute to BPH progression by triggering a localized inflammation [47]. A drop in AR expression in prostatic luminal cells followed by a rise in epithelial cells results in local inflammation mostly involving IL-1-dependent pathway. Moreover, stromal cells proliferation in transition zone is related to this localized inflammation via recruitment of macrophages in C-C Motif Chemokine Ligand 3-dependent mechanism [48–50] (Fig. 3).

A recent study by Wambier et al. has hypothesized that SARS-CoV-2 infection may be androgen-mediated. It has been suggested that TMPRSS2, which is a serine protease

essential for priming of the viral spike protein, requires AR activity for its gene transcription [51] (Fig. 3). Male patients with androgenic alopecia appear to be at greater risk of developing severe cases of COVID-19 and hence, hospitalization supports the hypothesis that COVID-19 is androgen-mediated [52, 53].

As mentioned before, AR are widely expressed in both epithelial and stromal cells of the prostatic tissue and play a major role in the development of BPH [43, 44]. Moreover, infection with SARS-CoV-2 seems to be androgen-mediated [51]. Thus, given that AR play a pivotal role in pathophysiology of BPH, one can conclude that causing progression of BPH may be a complication of COVID-19 and further studies should be conducted to investigate this possibility (Fig. 3).

It has been shown that high levels of DHT play a major role in pathophysiology of BPH; thus, decreasing the level of DHT through inhibition of 5-alpha reductase enzyme with agents such as finasteride and dutasteride is a key therapeutic option proposed for BPH treatment [54, 55].

Adamowicz et al. has suggested that 5-alpha reductase inhibitors (5-ARIs) impair the ability of the lungs in regeneration through augmenting the androgen levels in the epithelium of the lungs [54]; thus, it has been hypothesized that patients taking 5-ARIs such as finasteride and dutasteride have more propensity to develop COVID-19 and they may develop more severe cases.

On the other hand, a new study has also revealed that using 5-ARIs may be associated with less severe symptoms of COVID-19, although it may take weeks to reach an effective level in order to decrease DHT [56, 57]. However, caution should be exercised when attempting to draw conclusions about the mechanism of action and efficacy of these drugs that have variable effects on multiple tissues.

The results of previous studies revealed that pretreatment with finasteride reduced the levels of systemic cytokines and pro-inflammatory mediators such as macrophage inflammatory protein-1b and TNF- α released from isolated alveolar macrophages, and increased estradiol levels [58, 59]. These results suggest that inhibition of 5-alpha reductase leads to the conversion of testosterone to 17beta-estradiol, which produces salutary effects on the immune response.

Therefore, it can be concluded that the use of these inhibitors on the one hand can result in the deterioration of the COVID-19 progression by increasing androgens, and on the other hand, contribute to the better functioning of the immune system by reducing DHT, increasing estradiol production, and regulating immune responses (Fig. 3).

Overall, controversy exists regarding the role of androgen pathways in the pathophysiology of COVID-19 and this

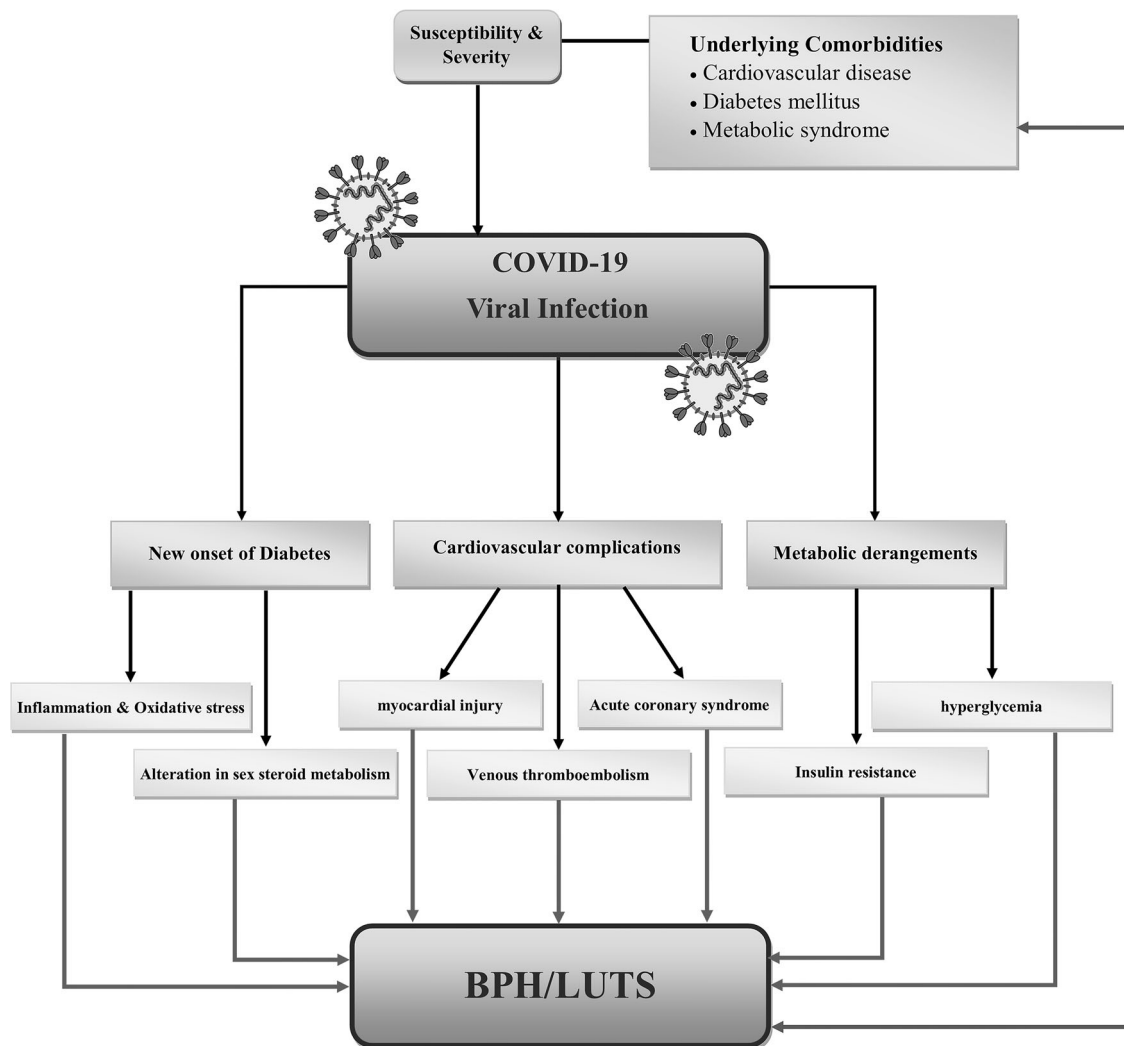


Fig. 4 Bidirectional interaction between BPH and COVID-19. Benign prostatic hyperplasia (BPH) was considered as a possible comorbid condition for COVID-19, due to high prevalence of underlying comorbidities (cardiovascular disease, diabetes mellitus, and

metabolic syndrome) in older men with BPH. New onset of diabetes, cardiovascular complications, and metabolic derangement may lead to BPH development as consequences of SARS-CoV-2 infection.

should encourage future studies to clarify the possible effect of anti-androgens on COVID-19 patients.

Evidence for the possible role of diabetes, cardiovascular dysregulation, and metabolic syndrome (MetS) in BPH aggravation and SARS-CoV-2 infection as a potential culprit

The possible association between some metabolic disorders including diabetes, cardiovascular diseases, and MetS and development of LUTS has been extensively studied. There is evidence of a propensity for development of BPH and LUTS in patients with diabetes. This can be explained by some factors associated with diabetes-induced hyperglycemia such as proliferation in prostate gland induced by insulin and related trophic factors, sex steroid hormonal

change, provoking inflammation and oxidative stress [60]. Furthermore, males diagnosed with hypertension appear to be at a greater risk of more severe LUTS compared to the ones without hypertension [61]. Besides, MetS, which is defined as a set of metabolic abnormalities such as high visceral adiposity and insulin resistance, is a common condition in patients with BPH and LUTS and the majority of the studies support the hypothesis that there seems to be an association between MetS and BPH and its related LUTS [62]. Although the exact underlying mechanism is not fully determined, probable culprits are sex-related hormonal change, systemic inflammation, insulin resistance, and aberrant lipid profile [63].

ACE2, which is the main entry receptor for SARS-CoV-2, is found throughout the metabolic organs such as adipose tissue and pancreatic beta cells, raising concerns regarding

the possibility of key metabolic organs involvement by the virus and resulting in new onset or exacerbation of pre-existing metabolic conditions such as diabetes. Interestingly, there are case reports of newly detected diabetes in patients infected with SARS-CoV [64]. Thus, these findings suggest that COVID-19 may deteriorate pre-existing metabolic abnormalities or even lead to new onset ones including diabetes [65].

Studies have found that patients with an underlying cardiovascular disease are more susceptible to worse outcomes of COVID-19 if infected. Moreover, studies have shown that COVID-19 can cause venous thromboembolism, acute coronary syndrome, and myocardial injury [66].

Taken together, the hypothesis that SARS-CoV-2 can result in new onset comorbid conditions such as diabetes and cardiovascular diseases or exacerbate the previously diagnosed comorbidities has gained recognition. Since these comorbidities are considered a risk factor for developing LUTS and BPH and their pathophysiology are connected in some ways, these findings suggest a potential route for development of LUTS and BPH secondary to exacerbation or new onset development of comorbid metabolic conditions and further studies should investigate this possibility (Fig. 4).

Conclusions and future prospective

The pandemic caused by the new coronavirus represents an extraordinary scenario in modern medicine that affects many aspects of daily healthcare. Since BPH has a high prevalence and is more common in older men who are more prone to COVID-19, we suggest a closer monitoring of older patients who are more susceptible to both BPH-related LUTS and also COVID-19 infection during this pandemic.

In general, BPH and its related LUTS progress slowly over a long period of time. It is demonstrated that the chance of presenting with acute urinary retention (AUR) in a male diagnosed with moderate-to-severe LUTS is around 0.6–1.8% per year, with a similar risk of developing infections and bladder stones [67, 68]. Therefore, this offers a rationale for monitoring the progression of symptoms of patients with BPH and LUTS during the COVID-19 pandemic.

The observation of patients with BPE is largely consisted of several aspects. We recommend the use of available questionnaires such as IPSS to identify the degree of bother [69]. As elevated serum PSA level is one of the most proven predictors of AUR episodes in patients with BPH, checking the serum PSA during and after pandemic in patients with old age affected by COVID-19 seems to be reasonable [70].

There are no studies investigating the potential of BPH progression as a complication of SARS-CoV-2 infection at

the present time and only a few studies have proposed BPH management during the SARS-CoV-2 pandemic. However, our literature review showed that different mechanisms such as ACE2 signaling alteration, AR-related mechanisms, inflammation, and metabolic derangement might lead to aggravation of BPH-related LUTS and its complications (e.g., AUR) over and after the course of infection with SARS-CoV-2.

Overall, since infection with SARS-CoV-2 seems to be an unraveled challenge for the human being, a deeper investigation regarding the possibility of COVID-19 leading to exacerbation of BPH symptoms and worsening of the previously diagnosed condition may help the scientists and clinicians discover novel mechanisms of infection of this disease in addition to better management of it.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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