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Unveiling prostatic inflammation to optimize management of lower urinary tract symptoms: a discussion with experts

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Benign prostatic obstruction (BPO) and associated lower urinary tract symptoms (LUTS) are common conditions in men, which increase in frequency and severity with age, and have a significant impact on quality of life. Chronic prostatic inflammation is increasingly being recognized as a key component of BPO. This may lead to new targets for the management of BPO/LUTS. This podcast is based on presentations from a symposium titled 'Unveiling prostatic inflammation to optimize LUTS management' held at the European Association of Urology 2023 Congress. The presenters outline evidence of a role for prostatic inflammation in the development and progression of BPO/LUTS, approaches to the identification of biomarkers of inflammation, and the implications of prostatic inflammation for the optimal management of BPO/LUTS.

Tweetable abstract: Inflammation is a key driver for BPH development and progression. *Serenoa repens* hexanic extract targets prostatic inflammation. Patients prefer less invasive management options with a low risk of adverse events.

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Keywords: benign prostatic obstruction • inflammation • lower urinary tract symptoms • metabolic syndrome • phytotherapy • podcast

Introduction

Alison Taylor

Hello and welcome to this podcast, which focuses on presentations and discussions from a symposium titled 'Unveiling Prostatic Inflammation to Optimize Lower Urinary Tract Symptom Management' that was held at the European Association of Urology Congress in Milan, Italy, in March 2023. The symposium was supported by Pierre Fabre. My name is Alison Taylor, and I'm present on behalf of Springer Healthcare France. Today, I will be speaking with Professor Mauro Gacci (Associate Professor at the Department of Minimally Invasive and Robotic Urologic Surgery and Kidney Transplantation, University of Florence; Careggi University Hospital in Florence, Italy), Professor Cosimo De Nunzio (Associate Professor at the Department of Molecular and Clinical Medicine, Faculty of Medicine and Psychology, Sapienza University of Rome, and Consultant Urologist at the Division of Urology at the Sant'Andrea Hospital in Rome, Italy), and Professor Stavros Gravas (Professor of Urology at the Medical School of the University of Cyprus, Nicosia, Cyprus). Hello, everyone. Please introduce yourself.

Dr Gacci

Good morning. I'm Professor Gacci and I'm Professor at the University of Florence and Careggi Hospital in Florence. I'm also the Chair of the Office of Education of the Société Internationale d'Urologie, and a member of the panel of the EAU (the European Association of Urology) guidelines of non-neurogenic lower urinary tract symptoms, including BPO [[benign prostatic obstruction]].

Dr De Nunzio
My name is Cosimo De Nunzio. I'm an Associate Professor of Urology at Sapienza University of Rome, and Editor-in-Chief of *Prostate Cancer and Prostatic Diseases*.

Professor Gravas
I'm Stavros Gravas. I'm Professor of Urology at the University of Cyprus. I am the Secretary General of Société Internationale d'Urologie, and I was the Chairman of the European Association of Urology guidelines panel on male LUTS [[lower urinary tract symptoms]] from 2013 until 2022.

Alison Taylor
In this podcast, we'll be discussing the role that prostatic inflammation may play in the development and progression of benign prostatic obstruction (also known as BPO) and associated lower urinary tract symptoms (or LUTS), and the implications of this for the management of these conditions. We'll be using a question-and-answer format to lead the discussion.

Role of prostatic inflammation in BPO/LUTS development & progression
Alison Taylor
Let's begin by defining the role of prostatic inflammation in the development of BPO. Dr Gacci, what are your thoughts on the causes of this inflammation?

Dr Gacci
So, inflammation is responsible for several chronic disease, including cardiovascular disease, including several cancers, and, in particular for our presentation, inflammation is directly related also to the development and progression of BPO and lower urinary tract symptoms [1]. Several factor can start the inflammatory process within our prostate, in particular, usually infection also in young people that activate this at the beginning, but also hormone alteration that is frequently related to the aging of the men, but also autoimmune disorders or immunological defect, like for example during a severe infection of people [1]. Also, another distinct but [[*sic*]] urinary reflux is another important issue, and also diet and lifestyle can be determinant to the development and then the progression of the inflammation [1]. When we have this pathogenetic mechanism, usually there are two main modification within the prostate, cellular, and humoral. Cellular means that within the prostate, several cells, including B- and T-cells lymphocyte but also macrophages, enter in the prostatic tissue and create the inflammatory infiltrate within the tissue. Then, these cells start to produce several humoral cytokines and chemokines, like interleukin 2, interferon gamma, or TGF [[transforming growth factor]] beta, that has two main activity [1]. The first is to maintain the chronic process within the prostate, and so becoming from an acute phenomena to a chronic phenomena, and then activate the fibromuscular cell within the prostate to bring the epithelial and stromal transdifferentiation and proliferation that bring a normal prostatic gland/normal prostatic tissue to the development and the progression to a BPH [[benign prostatic hyperplasia]], so an histological proven modification of structure of the glands. And this, in clinical effect, means the growing and the progression of the severity of low urinary tract symptoms [2–4].

Alison Taylor
Can you expand on metabolic syndrome as a possible cause of prostatic inflammation?

Dr Gacci
Metabolic syndrome is a chronic disease that is frequently related to the aging of the population, and more aged population usually experienced dyslipidemia or hypertension or diabetes or the improvement [[*sic*, increase]] of the fat, so the improvement [[*sic*, increase]] of the waist circumference; all these items means together metabolic syndromes. So when patients suffer of one or two of these issue, have usually smaller lower urinary tract symptoms and usually small prostate without inflammation [5]. When we have the coexistence of some of these factors that usually, during the elderly, the aging of the patients, can coexist, so patients that start with a small hypertension then become with an obese patients then become patients with diabetes. So when you have three or more of these items, and so you have patients with a metabolic syndrome, you have a dramatic change in the grow of the prostatic volume [6]. So you start from 40 to 60 prostatic volume to above 60, 80 or 100, and you have this that is directly related to the more inflammation within the prostate [5–8]. So more metabolic factors you are within the prostate,

more inflammation you are within the prostate [6]. Interestingly, more metabolic syndromes factor you have in single patients and more severe urinary symptoms you have. This demonstrated that the link between metabolic syndrome and the grow [5–8] and progression of prostate and the worsening of urinary symptoms can be driven by prostatic inflammation [6].

Alison Taylor

The evidence for a role for prostatic inflammation in the development and progression of BPO seems quite convincing; however, is there any evidence to the contrary?

Dr Gacci

So, there are some publication that demonstrate that if we have the capability to control the inflammation within the prostatic tissue, we have a reduction of the inflammation within the tissue that finally hesitated [[*sic*, resulted]] in better control of the urinary symptoms [9]. That's the reason why several drugs can act directly on inflammation and can improve urinary symptoms and quality of life by only reducing the prostatic inflammation. That means that, as compared to the past, we don't have to achieve reduction overall of the prostatic volume when we treat patients or an improvement of urinary flow rate. This prostatic volume and flow rate has been landmark of success of any treatment during the last 20 years, but nowadays, we consider that strong effectiveness of a medication/of a procedure/of a minimally invasive device in reducing the prostatic inflammation can strongly improve both urinary symptoms and quality of life of our patients.

Alison Taylor

Thank you Dr Gacci. Your last comment leads us to the next part of our discussion - the implications of prostatic inflammation for the management of LUTS. Dr De Nunzio can you outline the standard drug treatments for BPO/LUTS and their impact on prostatic inflammation?

Dr De Nunzio

The current pillars of drug treatments for LUTS are alpha-blockers, 5-alpha reductase inhibitors, antimuscarinics, beta3 agonists, and PDE5 [[phosphodiesterase type 5]] inhibitors, vasopressin analogues, and phytotherapies. Unfortunately, alpha-blockers and 5-alpha reductase inhibitors, which are the mostly prescribed drugs used to manage patients with lower urinary tract symptoms and BPH, have no anti-inflammatory activity and so their efficacy may be limited in patients with a moderate or severe prostatic inflammation [10]. This is really important in clinical practice because we know that patients with prostatic inflammation present with a major risk of clinical progression, a major risk of acute urinary retention, and need of surgery [2].

Approaches to targeting prostatic inflammation

Alison Taylor

What approaches would you recommend to targeting prostatic inflammation?

Dr De Nunzio

In clinical practice currently, we can consider three different approaches – conservative management, medical treatment or surgical treatment. Regarding the conservative treatment, we know the importance of physical activity and lifestyle. Physical activity can reduce prostatic inflammation through several mechanisms, including the release of different cytokines, mostly a reduction in the level of interleukin 8 and increase in the level of interleukin 10 [11]. Physical activity has, of course, another important role in patients with metabolic syndrome. Metabolic syndrome is considered one of the key driver in the development/progression of prostatic inflammatory infiltrates. So, it's important to reduce the risk of metabolic syndrome through physical activity, to possibly reduce the level of prostatic inflammatory infiltrates. Regarding surgery, we know that transurethral prostatic resection is still considered as the gold standard to surgically manage patients with LUTS and BPH; however, the study on the relationship between TURP [[transurethral resection of the prostate]] and inflammation are still controversial. What we know is that from one side, patients with prostatic inflammation presented a major risk of long-term recurrence but, on the other side, it is evident that patients with prostatic inflammation mostly benefit from TURP and presented a lower risk of persistent storage symptoms after treatment [12].

Alison Taylor
And what about medical treatment options?

Dr De Nunzio
So, there are several drugs that present anti-inflammatory activity and have been evaluated on LUTS and BPH patients. For example, the PDE5 inhibitors tadalafil and vardenafil have been shown in anti-inflammatory activity but only in animal [13] and in vitro studies [14], while there is no evidence in clinical trial. There are some evidence on the non-steroid anti-inflammatory drugs [15] but, due to their important adverse events, they have never been used or tested in clinical practice. Various phytotherapies have been used, including the extract of *Serenoa repens* with hexanic extract, that is the mostly studied.

Alison Taylor
Can you outline the mechanism of action of HESr [[hexanic extract of *Serenoa repens*]]?

Dr De Nunzio
Hexanic extract of *Serenoa repens* present several mechanism of action. Probably the most important are related to the antiproliferative effect or the anti-inflammatory effect. The anti-inflammatory effect may be related to different mechanism. One is related to the ability to inhibit the activity of the lipoxygenase and so to prevent the production of several metabolites, mostly cytokines [16]. And, it also has been shown to modify the activity of the leukocytes and to modulate the release of several inflammatory cytokines, which are related to the development and progression of prostatic inflammatory infiltrates [17,18].

Alison Taylor
Those data are intriguing. Is there also clinical evidence that HESr has anti-inflammatory activity and associated efficacy in treating LUTS?

Dr De Nunzio
Several studies are available. One of the most important is the Latil study, a double-blind, randomized study of men with BPH and LUTS [19]. They were treated with 3 months of hexanic extract versus tamsulosin, and hexanic extract was able to significantly reduce the expression of several inflammatory mediators in the urine [19]. So, while both treatment were effective in terms of urinary symptoms, only hexanic extract of *Serenoa repens* was able to significantly reduce the rate of gene expression of various inflammatory mediators. Another important study, coordinated by Professor Gravas, supporting that the hexanic extract was able to reduce prostatic inflammation evaluated using Irani scores versus baseline and versus patients not receiving treatment [20]. Finally, a recent systematic review focusing on about 6,000 patients and including about 27 randomized clinical trial and prospective observational trial clearly showed as the hexanic extract was more effective than placebo, similar efficacy to tamsulosin, and similar efficacy to the short-term treatment with 5-alpha reductase inhibitors [21].

Identifying biomarkers of prostatic inflammation to guide treatment of BPO/LUTS

Alison Taylor
Thank you, Dr De Nunzio. As you mentioned, there are a number of treatments available for BPO and LUTS. We now turn to the challenge of identifying the right treatment for the right patient. Professor Gravas, what are your thought on this?

Professor Gravas
It is true that we face a challenge in our daily practice because patients with LUTS have different needs due to the multifactorial etiology of symptoms, the different baseline characteristics – not all patients are the same. We have men with small prostates, with big prostates, with low PVR [[post-void residual]], with high PVR, with a middle lobe, without a middle lobe, and so on. And, in addition, patients may have different expectations from treatment. So when we assess men with LUTS, we need to identify the cause of patient's symptoms, define their clinical profile, and understand their values and preferences in order to provide a more personalized care.

Alison Taylor
Do we currently have the information we need to provide such personalized care?

Professor Gravas

That's a good question. We all agree that there is a need for individualized treatment of men with LUTS, and the concept of "one size fits all" is not applicable to the management of male LUTS. The limitation of the available data or the available randomized controlled trial (they have the highest level of evidence) is that they provide mean results for the average patient from a defined population, and even the *post-hoc* analyses help us to understand treatment response in a subgroup of patients. What we need is studies that focus on the individual patient level and investigate the impact of multiple baseline parameters on disease outcomes. So, a first effort has been the application of clinical trial simulations at the individual patient level, and this clinical trial simulation can run several virtual scenarios [22]. In addition, a novel predictive modelling study has recently evaluated the aggregated contribution of baseline characteristics to treatment response for the individual profiles of disease progression [23]. But since we talk about prostatic inflammation, and prostatic inflammation does play a significant role in the development and progression of LUTS, we need to find also molecular and clinical biomarkers that maybe help us to identify patients who have prostatic inflammation and, as a result, patients who will respond to a specific treatment related to prostatic inflammation.

Alison Taylor

Has there been any recent progress in this regard?

Professor Gravas

Yes. We have been developing a nomogram to predict the risk of prostatic inflammation in men with LUTS. This is a multicenter trial and it included patients with LUTS who underwent prostatic surgery for benign prostatic obstruction or a transrectal biopsy. So baseline demographic and clinical characteristics of the patients are being correlated with histological outcome, and we analyzed 15 baseline parameters as predictors of prostatic inflammation. We hope that we are going to release the final results very soon.

Alison Taylor

That sounds very interesting. In the meantime, what do we know about patient preference for treatment for LUTS and BPO?

Professor Gravas

We performed a systematic review on the published evidence on the values and preferences of men with LUTS regarding investigation and therapies [24]. So the results showed that men prefer medical treatment options that improve urgency incontinence and nocturia, reduce the risk of surgery or developing acute urinary retention. Patients prefer less invasive management options with low risk of adverse events. This is normal, it's human. And there is also a preference for surgery when the surgery has a high rate of success and a low risk of complications, and men with a high baseline level of sexual activity are more concerned about the risk of postoperative sexual dysfunction.

Alison Taylor

What do you think are the most important points to consider regarding patient preference for treatment?

Professor Gravas

Patients' and clinicians' expectation of outcomes may differ. We should always take that into account. So patients may prefer less effective treatment options if they have a lower risk of complication or provide a faster return to normal activities. We, as clinicians, sometimes we focus more on durability. For this reason, we need to discuss the available therapies with all our patients, and objectively inform them on the efficacy and potential adverse events of these treatment options.

Conclusion

Alison Taylor

Well, I think that's all we've got time for. We've covered a number of important issues that, I hope, have expanded understanding on the role of prostatic inflammation in LUTS and BPO, the need to identify this pathology (via biomarkers, where possible) and the importance of incorporating treatments for prostatic inflammation into the management algorithm for these common conditions. Thank you very much to everyone who took part.

Author contributions

Mauro Gacci, Cosimo De Nunzio and Stavros Gravas were involved in the preparation and presentation of information at the symposium, the recording of the podcast, and the writing of the associated manuscript.

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