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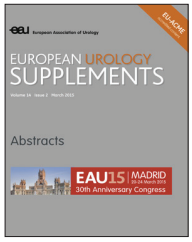

European Association of Urology

Editorial

Inflammation and Prostatic Diseases: From Bench to Bedside

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Benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS) is the most commonly diagnosed urologic disease in older men. BPH is characterised by enlargement of the prostate gland due to age-related progressive proliferation of stromal and glandular prostatic cells [1,2]. The overall prevalence of BPH in the male population is reported to be >70% at age 60 yr and >90% at age 70 yr [3,4]. Histologically confirmed prostatic inflammation is a common finding in biopsy and surgical specimens from elderly male patients with BPH and is reportedly present in 43–77% of samples [5–7]. Due to increased longevity of the male population and more thorough clinical investigation (earlier consultations and screening programmes), the BPH diagnosis is becoming increasingly common [8].

Although BPH aetiology remains somewhat uncertain, a number of factors are known to be involved in its pathogenesis. BPH is clearly associated with the ageing process. Other risk factors include hormonal alterations (presence of testicular androgens), a proinflammatory environment (insulin resistance, secondary hyperinsulinaemia, and the metabolic syndrome), increased sympathetic nerve activity, and local (prostatic) inflammation. This was the subject of a recent review [9]. In particular, the role of chronic prostatic inflammation has generated much interest in the past decade [2,9–11]. Patients with BPH and chronic inflammation have larger prostate volumes, are predisposed to more severe LUTS, are more likely to develop acute urinary retention, and have a poorer response to conventional medical therapy than patients without inflammation [2,9,11]. Although histologic evaluation for prostatic inflammation would be the ideal confirmatory diagnostic procedure, it can be performed only in patients who have undergone biopsy for suspected prostate cancer. Other predictors of chronic inflammation investigated have included prostatic calcifications, prostate volume, LUTS severity, symptoms, poor response to medical treatment, and urine and serum biomarkers [9,12].

Biomarkers represent a potentially interesting noninvasive alternative to biopsy for detecting chronic prostatic inflammation. Prostate tissue often contains increased inflammatory infiltrates, including T cells and macrophages [11,13]. Cytokines are key mediators of inflammation and may play an important role in the initiation and progression of BPH. Proinflammatory cytokines with potential application as predictive biomarkers for BPH include interleukin-8 in seminal plasma; monocyte chemotactic protein 1 in prostatic secretions; and urinary biomarkers CCR7, CTLA4, ICOS, and CD40LG. Each of these urinary biomarkers has been shown to be upregulated at the messenger RNA level in patients with chronic prostatic inflammation [12]. Recently, Engelhardt and colleagues found a high incidence of prostatic calcification in patients with obstructive BPH; the chronic inflammatory reaction of the prostate gland appeared to be triggered by the cytokine-induced inflammatory effect of tumour necrosis factor α [14]. The pivotal role played by chronic prostatic inflammation in the pathogenesis and progression of symptomatic BPH suggests potential benefits with use of novel anti-inflammatory medical therapies in this clinical setting.

At the European Association of Urology (EAU) congress in 2013, evidence was reviewed implicating inflammation as a largely neglected factor in BPH and LUTS [15]. In the current communication series, recent evidence pertaining to BPH pathophysiology was evaluated with a focus on the role of prostatic inflammation in the development and progression of BPH [16]. Key clinical findings from the REDUCE and MTOPS studies were reviewed [17], and the potential for new treatments with anti-inflammatory activity in the prostate was discussed. There is evidence of clinical benefit with agents that inhibit cyclooxygenase (COX) in the arachidonic acid cascade (eg, nonsteroidal anti-inflammatory drugs and COX-2 inhibitors), although their use may be limited by safety issues.

In 2013, the role of the phytotherapeutic agent *Serenoa repens* was reviewed with a focus on its anti-inflammatory

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effects [18,19]. At that juncture, the PERMIN study had just commenced. PERMIN was a randomised controlled trial comparing hexanic extract of *Serenoa repens* (Permixon; Pierre Fabre Médicament, Castres, France) with tamsulosin in patients with moderate to severe BPH-related LUTS. It was the largest randomised clinical trial specifically designed to compare the prostatic anti-inflammatory effects of BPH treatments using non-invasive methods; full results have recently been published [20]. At the EAU 2015 congress, some key findings from PERMIN were re-interpreted for their clinical relevance [21].

Many brands of *Serenoa repens* produced from different botanical sources and using a variety of extraction procedures are available worldwide. Although the hexanic lipidosterolic extract is the most widely researched product, it is useful to know whether other brands are comparable in terms of efficacy and safety [22]. The European Medicines Agency recently concluded that available evidence for the hexane extract supported its use as "a well-established medicinal product with recognised efficacy and acceptable safety," whereas data for the two other main extracts (ethanolic and supercritical CO_2 extracts) did not support such a conclusion [23].

Finally, a large body of evidence supports the concept that prostatic inflammation plays a key role in the pathogenesis and progression of BPH. This has opened the gateway to new avenues of treatment based on targeting inflammatory mediators. *Serenoa repens* has exhibited anti-inflammatory effects in pharmacologic studies, and the hexanic extract has now produced positive results in a well-controlled clinical trial. Future studies are expected to confirm these positive clinical findings.

Conflicts of interest

Javier Burgos has received fees for serving as a speaker and/or consultant for Astellas, Janssen, Pierre Fabre, and Sanofi within the past 3 yr.

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