

## INVITED REVIEW

# Highlights on the Canine Prostatic Specific Esterase (CPSE): A diagnostic and screening tool in veterinary andrology

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**Abstract**

In the last years, the need to look for an accurate and precise diagnosis of prostatic diseases in dogs has grown. Among other diagnostic tools, the seric CPSE has been studied and identified as a valid and specific biomarker for prostatic disorders, since it can result significantly more elevated in dogs affected by several prostatic abnormalities, such as benign prostatic hyperplasia, bacterial prostatitis and prostatic carcinoma. Therefore, dosing CPSE in serum represents a new diagnostic and screening tool. Dosing CPSE in everyday clinical practice has three objectives: (a) the diagnosis of benign prostatic hyperplasia; (b) the preventive screening of prostatic disorders in healthy dogs; (c) the medical follow-up in subjects with prostatic disorders during and after medical therapy. Neither circadian rhythms nor transrectal palpation performed during the andrological examination do affect CPSE. A sexual rest of at least 24 hr before dosing CPSE is recommended as it is affected by ejaculation.

**KEYWORDS**

Benign Prostatic Hyperplasia, CPSE, Dog, Preventive Medicine, Prostate, Prostatitis

## 1 | INTRODUCTION

Prostatic abnormalities in dogs are very common (Cunto, Mariani, Anicito Guido, Ballotta, & Zambelli, 2019) and the possibility to diagnose them thanks to the availability of new tools, allows the identification of an increasing number of cases (Alonge, Melandri, Aiudi, & Lacalandra, 2018). In a recent epidemiological study, retrospectively analysing routine ultrasonographic evaluations (1,003 dogs examined), irrespective of the reason for the veterinary consultation, 47.5% of the dogs showed at least one abnormal prostatic finding. Moreover, the prevalence is higher in dogs with long life-expectancy than in subjects with short life-expectancy, calculated based on their breed (Mantziaras, Alonge, Faustini, & Luvoni, 2017). Age-related changes of the prostate in dogs have already been documented in literature (Mantziaras et al., 2017; O'Shea, 1962).

Among the prostatic abnormalities, the benign prostatic hyperplasia (BPH), primarily non-inflammatory enlargement of the accessory gland in the intact dog, is the most frequently represented one with a prevalence between 46% and 55.3% of the patients (Dorfman & Barsanti, 1998). Testosterone and oestrogen play a decisive role in this age-related para-physiological condition and in its pathogenesis. This disease affects over 80% of dogs at 6 years of age and 95% at 9 years of age (Berry, Coffey, Strandberg, & Ewing, 1986). It is followed by acute and chronic prostatitis, with a prevalence of 28%–38.5% (Dorfman & Barsanti, 1998). Numerous small cysts disseminated in the glandular parenchyma can accompany BPH, even if prostatic cysts can represent a peculiar pathological entity with a prevalence between 2.6% and 14% (Black, Ling, Nyland, & Baker, 1998; Dorfman & Barsanti, 1998). Prostatic neoplasia is almost rare in dogs (2.6%–3.5%), but frequently malignant and

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generally fatal (Axiak & Bigio, 2012; Dorfman & Barsanti, 1998; Ravicini et al., 2018). Also prostate abscesses and squamous metaplasia can be observed (Dorfman & Barsanti, 1998; Johnston, Root-Kustritz, & Olson, 2001; Polisca, Troisi, Fontaine, Menchetti, & Fontbonne, 2016).

An important recent interest in Veterinary Medicine is represented by the diagnosis of prostatic disorders, given to the greater attention that the owners dedicate to their pets' health, as well as to the increase in medical availability of diagnostic tools and therapies. In recent years, many researches have been conducted to identify prostatic disorders as early as possible (Alonge, Melandri, Leoci, Lacalandra, & Aiudi, 2018b; Levy, Nizanski, von Heimendahl, & Mimouni, 2014; Mantziaras et al., 2017).

## 2 | THE CHOICE OF A PROSTATE BIOMARKER IN CANINE ANDROLOGY

Serum canine prostatic-specific esterase (CPSE) has been recognized as a valid and specific biomarker for canine prostatic disorders because its content is higher in the serum of dogs affected by different prostatic alterations such as BPH, bacterial prostatitis and prostate cancer (Beining et al., 2020; Bell et al., 1995; Gobello, Castex, & Corrada, 2002; Holst et al., 2017; Levy, Fontbonne, & Derre, 2009; Levy et al., 2014; Pinheiro et al., 2017; Teinflat, Miller, Loupal, & Thalhammeret, 2000; Weaver, 1981; Wolf et al., 2012). In physiological conditions, the CPSE is secreted into the lumen of the prostate ducts, and mainly remains in the prostate gland (Dearakhshandeh et al., 2020); conversely, when the prostate gland is altered, proteins of prostatic origin, such as CPSE, can be found in blood (Gobello et al., 2002).

In seminal plasma, the CPSE is the most abundant protein and exerts its physiological effects on spermatozoa modulating their function (Schafer-Somi & Palme, 2016; Zelli et al., 2016). The CPSE was identified in the seminal fluid and in prostatic cells, either normal, or hyperplastic or neoplastic ones (Frenette, Dube, & Marcotte, 1985; Isaacs & Coffey, 1984; Isaacs & Shaper, 1983, 1985; McEntee, Isaacs, & Smith, 1987). The prostate is the only organ producing CPSE (Acquino-Cortez et al., 2017; Chapdelaine, Dube, Frenette, & Tremblay, 1984; Dube, Lazure, & Tremblay, 1986). The post-acrosomal zone and the tail of the ejaculated spermatozoa show CPSE given its bind to specific membrane phosphorylcholine. Conversely, the epididymal spermatozoa do not show the enzyme (Isaacs & Coffey, 1984). As a sperm-binding protein, the CPSE seems to be involved in events related to sperm fertilization (Mogielnicka-Brzozowska, Kowalska, Fraser, & Kordan, 2015) and, given to its ability to bind to zinc ions, it turns out to be a multifunctional molecule (Acquino-Cortez et al., 2017; Chapdelaine et al., 1984; Dube et al., 1986). Studies are warranted to better clarify the specific role of the CPSE in the fusion process between oocyte and spermatozoa (Mogielnicka-Brzozowska, Sowinska, & Fraser, 2017).

## 3 | THE ROLE OF THE CPSE IN THE CANINE ANDROLOGICAL BREEDING SOUNDNESS EXAM

Serum CPSE assessment improves canine andrological diagnostics and it is useful in order to perform a complete breeding soundness examination of the dog, in addition to the new applications of traditional and doppler ultrasound (De Freitas, Pinto, Silva, & da Silva, 2015; Mantziaras, 2020; Rodak, Dzimira, Podolak, Płóciennik, & Nizański, 2018; Russo, Vignoli, & England, 2012; Zelli, Orlandi, Troisi, Cardinali, & Polisca, 2013).

In everyday practice, CPSE assessment is useful in three different purposes of the andrological clinical exam: first, as a diagnostic tool for prostatic disorders (Holst et al., 2017; Pinheiro et al., 2017); second, as a biomarker for the early screening of prostate health in dogs (Alonge et al., 2018b); third, to support the follow-up of patients suffering from prostatic diseases and undergoing to medical treatments (Sagols & Navarro, 2014).

Higher CPSE values were observed in dogs affected by Benign Prostatic Hyperplasia (BPH), prostatitis or prostate cancer (Bell et al., 1995; Gobello et al., 2002; Wolf et al., 2012). Significant results were obtained with the quantification of the CPSE in the identification of subjects clinically affected by BPH (Holst et al., 2017). In this case, the diagnostic threshold at 90 ng/ml is predictive of disease in subjects with the presence of evident clinical signs and with an organ volume 2.5 times higher than the normal expected one ( $V_{ratio} > 2.5$ ) (Holst et al., 2017). Other authors previously reported higher CPSE values in dogs with BPH than in normal ones, or in animals affected by bacterial prostatitis and prostatic carcinoma (Gobello et al., 2002). Different studies found no differences between CPSE serum concentrations in dogs with BPH and in subjects affected by bacterial prostatitis and carcinoma, an event that was attributed to the existence of a concurrent BPH (Bell et al., 1995; Pinheiro et al., 2017). Even if serum CPSE activity was significantly higher in dogs with BPH than in healthy dogs, no significant differences were found among dogs suffering from BPH, bacterial prostatitis and prostatic carcinoma (Bell et al., 1995; Gobello et al., 2002). Bell and colleagues reported a non-statistically significant trend for mean serum CPSE concentrations being higher in dogs with carcinoma than in healthy ones (Bell et al., 1995). The absence of statistical significance was possibly due to the low power of some comparisons or to the limited number of cases with the neoplastic diagnosis: the evaluation of some additional dogs might have revealed a statistically significant difference in mean values (Bell et al., 1995). Moreover, neoplastic cells likely express CPSE only rarely, possibly explaining the lack of any significant increase in serum CPSE concentration in patients with a prostatic cancer (Bell et al., 1995). The CPSE was in fact identified by immunohistochemical staining in only 2 of 14 dogs diagnosed with prostatic adenocarcinoma (Bell et al., 1995). Similar results were achieved in a previous study that detected CPSE in only 8 of 31 neoplastic prostate glands (McEntee et al., 1987). As a consequence, serum CPSE concentrations/activities alone may

not be enough to come to a definite diagnosis of prostatic adenocarcinoma; more researches on this aspect should be carried on before a definitive conclusion can be drawn (Bell et al., 1995).

To enhance a preventive screening for prostatic abnormalities in asymptomatic dogs, the CPSE threshold of 52.3 ng/ml has been defined (Alonge et al., 2018b). This results were usually associated with initial signs of prostatic alterations detectable by ultrasound (for altered eco-structure and/or margins, and/or for the presence of cysts), requiring further diagnostic investigations (Alonge et al., 2018b). In that study by Alonge et al. (2018b), in almost 60% of the enrolled subjects, although asymptomatic, ultrasound examination showed prostatic changes (altered eco-structure and/or margins, and/or the presence of cysts). Moreover, the real prostate volume in those subjects was at least 1.5 times higher ( $V_{ratio} > 1.5$ ) than expected (estimated on the basis of the bodyweight of each subject (Sannamwong, Saengklub, & Sriphuttathachot, 2012)). The observation was confirmed in subjects with normal prostate in which the CPSE value was statistically lower than in ill subjects (Alonge et al., 2018b). A preventive screening for prostatic disorders is therefore possible, allowing the early identification of those subjects, still asymptomatic, who need further diagnostic investigations or a closer follow-up. Thus, for this purpose, it was suggested to set the threshold value at 50 ng/ml to identify dogs usually presenting prostate ultrasonographic changes and a V ratio (ratio between actual and expected prostate volume) higher than 1.5 (Alonge et al., 2018b).

Finally, as CPSE is controlled by testosterone, it might represent a functional marker of the androgenic state of the dog and its response to any androgenic therapy, either by receptor antagonists or by 5- $\alpha$ -reductase inhibitors (Gobello et al., 2002). The medical treatment with osaterone acetate in dogs with subclinical BPH significantly decreases the concentration of CPSE (Sagols & Navarro, 2014). Further studies are warranted to confirm the use of this biomarker in the follow-up of subjects with clinically confirmed BPH undergoing medical therapy.

## 4 | THE CPSE DOSAGE AND POSSIBLE CONFOUNDING FACTORS

Some factors can alter the serum concentration of CPSE, and in daily clinical practice it is fundamental to know them, as they could lead to potential false diagnoses.

The CPSE concentrations are not affected by the bodyweight, thus its test is considered reliable in dogs of any size (Pinheiro et al., 2017).

No correlation was identified between CPSE and the expected prostatic volume, as the latter calculates the prostate size based on the bodyweight of each evaluated dog (Atalan, Holt, Barr, & Brown, 1999; Pinheiro et al., 2017).

A recent study shows that the CPSE does not undergo to circadian variations and trans-rectal palpation does not influence its concentration in serum (Loukeri & Claret, 2017).

However, ejaculation does influence the serum levels of CPSE (Alonge et al., 2020; Borges, Maenhoudt, Loukeri, Claret, & Fontbonne, 2018). In fact, ejaculation increases physiologically the vascular supply to the prostate (Alonge, Melandri, Fanciullo, Lacalandra, & Aiudi, 2018; Alonge, Melandri, Leoci, Lacalandra, & Aiudi, 2018a) and the CPSE stored in the gland is more abundantly removed (Alonge et al., 2020). Therefore, for the correct dosing and sound clinical interpretation of the results, a proper sexual rest of at least 24 hr is mandatory before the evaluation of the CPSE serum concentration (Alonge et al., 2020).

## 5 | THE IMPORTANCE OF SCREENING FOR PROSTATIC DISORDERS

Unfortunately, prostatic abnormalities in the canine population go often unnoticed in everyday situations and become more evident when the dog undergoes to diagnosis for suspected poor fertility (Polisca et al., 2016).

Some considerations on dosing CPSE in the monitoring of the state of health of the dog's prostate are noteworthy:

- in the breeding stud dog (a dog "intended to make a career") BPH and/or chronic prostatitis are more frequently recognized as they undergo more often to a complete andrological examination especially after some not successful matings;
- in any pet dog (any family dog) a screening for prostate disorders can early recognize BPH and/or chronic prostatitis which have the same high frequency as in the stud dogs, allowing further diagnostic investigations in asymptomatic subjects.

Applying routine screening programs for prostate health in dogs could lead to understanding of the real prevalence of prostatic diseases. Particularly, a non-invasive screening of the prostate health would be advisable especially as a part of a preventive medicine program of geriatric diseases in dogs (Mantziaras et al., 2017). Already at three or four years, the 40% of the canine intact male population is affected by BPH, 88% at six years and nearly 100% between seven and nine years (Lowseth, Gerlach, Gillett, & Muggenburg, 1990). However, the large majority of dogs affected by BPH do not and will never show clinical symptoms. Moreover, as in humans, the prostate size (and BPH severity) does not directly correlate with clinical symptoms (Teske & De Gier, 2013).

It was recently stated that there is a high probability of detecting prostate alterations, sonically evident regardless of the presence of clinical symptoms, in patients over 40% of the expected life, calculated according to the breed (Mantziaras et al., 2017). Moreover, it was reported that in 82.7% of dogs the enlargement of the prostate coexisted with other findings (Mantziaras et al., 2017). Among these, the concurrent presence of cysts was evident in 74.3% of dogs and this association was in agreement with other epidemiological studies that documented the most common prostatic diseases which may sooner or later threaten the well-being of a dog (Johnston

et al., 2001; Mantziaras, Alonge, & Luvoni, 2014). Thus, even if a primarily non-inflammatory enlargement of the accessory gland in the intact dog can be expected and considered an age-related para-physiological condition, all these findings prompt to suggest that in clinical practice, when a higher CPSE concentration or an enlarged prostate is diagnosed in a routine or screening exam, a more detailed evaluation of the organ should be performed. In a screening program, the CPSE concentration on its own should not be considered fully diagnostic, but as an objective parameter to suggest or strongly recommend to the owners the opportunity of a deeper instrumental evaluation.

## 6 | CONCLUSION

Veterinary practitioners should tell owners about the potential effects of ageing on the canine prostate gland. In clinical practice, to increase canine well-being, male dogs should receive the same attention normally paid to ageing bitches. In fact, BPH shares with cystic endometrial hyperplasia (CEH) some epidemiological and etiological features (Bigliardi et al., 2004; Melandri, Barella, & Alonge, 2019b; Melandri, Veronesi, Pisu, Majolino, & Alonge, 2019a; Moxon, Whiteside, & England, 2016; Niskanen & Thrusfield, 1998): they are under age and hormonal control, and often symptomless before they can be complicated by prostatitis and pyometra, respectively. At least over the 40% of the expected life, calculated according to the breed, even asymptomatic male dogs should start to be screened by CPSE dosage in order to promptly suggest to the owner to go further in a more sophisticated and expensive diagnostic investigation to prevent complications which may become life-threatening. The research on the correct management and therapy of prostatic diseases in dogs is still ongoing, but the current availability of different medical treatments highlights the need for the development of screening programs, with the final aim of avoiding the invasive option, i.e. surgical castration, putting an end to the reproductive career of a stud.

## ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTION

**Monica Melandri:** Conceptualization; Formal analysis; Investigation; Writing-original draft. **SALVATORE ALONGE:** Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing-original draft; Writing-review & editing.

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