Noninfectious Prostatic Diseases in Dogs

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ABSTRACT: The prostate—the only accessory gland of the genital tract in dogs—is under androgenic control. Common canine prostatic disorders include benign prostatic hyperplasia (BPH), prostatitis, cysts, and adenocarcinoma. BPH is a common age-related condition that occurs in 95% of male dogs by 9 years of age. The exact pathogenesis of canine BPH is not completely understood, although it is known that dihydrotestosterone is the key factor in stimulating prostate growth. Clinical signs of BPH include sanguineous preputial discharge, constipation, and tenesmus. Clinical signs respond to castration or to antiandrogenic treatment (e.g., finasteride), which inhibits conversion of testosterone to dihydrotestosterone (resulting in prostatic involution). A number of studies in stud dogs have demonstrated that certain antiandrogens may have clinical application without producing clinically adverse effects or changes in semen quality and fertility. Ultrasonography-guided biopsy facilitates the diagnosis. Prostatic adenocarcinoma is often difficult to diagnose in the early stages and is even more difficult to manage. Neither prostatectomy nor castration has been found to improve the quality of life or to effectively cure the disease. Serum and seminal markers have enhanced the early, noninvasive diagnosis of prostatic diseases, although further research is necessary to define their exact role in different disorders.

Benign prostatic hyperplasia (BPH) is a spontaneous, age-related condition that affects 95% of intact male dogs by 9 years of age. Treatment of BPH with antiandrogens has clinical application in stud dogs. Prostatic malignancy is uncommon.

The prostate—the only accessory sex gland in the intact male dog—is an androgen-dependent, ovoid-shaped, bilobed gland composed of glandular and stromal elements that encircle the urethra caudal to the neck of the urinary bladder. With increasing volume (as in older dogs), the prostate tends to move farther into the abdomen; in young dogs and those castrated at an early age, it resides within the pelvic inlet. The prostate contributes fluid to the first and third fractions of the canine ejaculate.

Prostate disorders (i.e., benign prostatic hyperplasia [BPH], prostatitis, cysts, squamous metaplasia, neoplasia, and their combinations) are common in male dogs. Many therapies are available for the different diseases; therefore, a specific diagnosis is essential for proper therapy and prognosis. This article briefly reviews noninfectious diseases of the canine prostate gland.

BENIGN PROSTATIC HYPERPLASIA

BPH—the most common disease of the canine prostate—is a spontaneous, age-related condition in intact male dogs. BPH increases with frequency almost linearly with age; close to 95% of dogs are affected by 9 years of age. BPH affects the prostate diffusely and causes it to expand dorsally. The disease begins...
as glandular hyperplasia in dogs as young as 2.5 years of age. Dogs older than 4 years of age with BPH tend to become cystic (cystic hyperplasia) as multiple small cysts form in the parenchyma. BPH occurs in two phases: glandular and complex. In dogs younger than 5 years of age, BPH is primarily glandular (i.e., mainly epithelial). In older dogs, the complex form, in which hyperplasia and areas of atrophic epithelium are present, is typically observed. 

Pathogenesis

BPH develops in males with intact testes and is age related. Its exact pathogenesis is not completely understood. Dihydrotestosterone (DHT), which is irreversibly converted from testosterone (T) by the action of 5α-reductase within prostatic epithelial cells, is accepted as a key hormone in stimulating enlargement of the canine prostate by enhancing growth in both stromal and glandular components. Dogs experience a moderate decline in circulating T, and DHT concentrations throughout adult life, while serum estradiol remains unchanged with age. Thus the growth of the prostate with advancing age takes place while there is a decline in the ratio of circulating androgen to estradiol. The role of estrogen in BPH has recently been recognized. Estrogens induce nuclear DHT receptors and thus may increase the sensitivity of the prostate to DHT. As dogs age, DHT concentration and receptors increase in prostatic tissue.

There are indications that pituitary hormones may also affect the development of BPH. Prolactin has been shown to regulate differentiation and proliferation of rat and human prostate epithelium, and prostate enlargement was observed in young human patients with untreated acromegaly. Growth hormone may stimulate prostate enlargement through a direct interaction with growth hormone receptors or enhanced plasma insulin-like growth factor–1 concentrations.

Clinical Signs and Diagnosis

Most cases of BPH are not associated with clinical signs. Intermittent, hemorrhagic or clear to light yellow urethral discharge and intermittent or persistent hematuria occur in some dogs. Although blood is frequently observed in semen samples and the volume of ejaculate is decreased, total sperm count and fertility are not affected by BPH. It is only when the prostate becomes large enough to compress the colon and interferes with defecation that serious effects result and rectal tenesmus and constipation may be present. Occasionally, ribbonlike stools are observed if the enlarged prostate compresses the rectum. Although urethral obstructive disease occurs in men with BPH, it is extremely rare in dogs. The most common complication of BPH in dogs is secondary bacterial infection of the gland, leading to prostatitis. Perineal hernias are less common complications.

Diagnosis of BPH is based on the presence of typical clinical signs and on detecting a uniform prostatic enlargement by palpation, radiography, and/or ultrasonography. The caudal/dorsal aspect of the prostate in most dogs can be palpated via the rectum, although the position of the prostate in the caudal abdomen depends on bladder distention, age, and disease. On digital rectal palpation, the hypertrophied prostate is found to be enlarged but symmetric, soft with a smooth contour, movable, and painless. Prostatic volume in affected dogs may be two to 6.5 times greater than that of normal dogs.

Hematologic and serum biochemical findings are unaffected by hyperplasia, while urinalysis and semen samples may be normal or contain blood without pyuria or bacteriuria. Samples for cytologic analysis and culture can be obtained by ejaculation, prostatic massage, or aspiration biopsy. Prostatic massage is performed by removing urine from the bladder, placing the tip of a urinary catheter in the prostatic urethra (using rectal palpation as a guide), gently massaging the prostate via the rectum or abdomen for 1 to 2 minutes, and aspirating material into the catheter.

The normal gland is not easily seen in survey radiographs but can be identified using retrograde contrast urethrocytography with bladder distention. Hyperplastic prostates are usually visible on survey abdominal radiographs as mild to moderate prostatic enlargements with dorsal displacement of the colon and cranial displacement of the bladder. The prostate is considered enlarged when the prostatic diameter, as visualized on the lateral radiographic view, is greater than 70% of the distance between the sacral promontory and the pubis. Ultrasonography allows for assessment of prostatic contour as well as parenchymal tissue. Ultrasonography usually shows an enlarged, uniformly isoechoic to hyperechoic prostate with occasional small areas of decreased echogenicity if cystic hyperplasia is present. Cavity areas are typically well defined and smoothly marginated.

Definitive diagnosis is based on histopathologic findings, although collection of prostatic cells by transrectal fine-needle aspiration, with or without ultrasonography-guided placement, has also proved to be a successful and simple method of diagnosis. Depending on the location of the gland and prostatic size, transabdominal aspiration is also possible. Needle aspiration should be avoided in dogs with abscessation since large numbers of bacteria may be seeded along the needle tract. Complications of aspiration are rare; occasionally, mild tran-
sient hematuria occurs. Needle core biopsy of the prostate can also be performed by transabdominal approach. Histologic evidence of mild chronic interstitial inflammation is common in BPH. The principal diagnostic differentials are chronic prostatitis and squamous metaplasia.

**Treatment**

Treatment of BPH is required only if related abnormal signs are present. The objective of treatment is to decrease prostatic size, which alleviates related signs. The most effective and standard treatment is castration. Canine prostatic size decreases by 50% within 3 weeks of castration and by 70% within 9 weeks. Castration is not appropriate for dogs required for breeding. Furthermore, castration is sometimes refused by owners and some older dogs may be at a high risk for surgical complications.

Various medical treatments are available for BPH, but none is currently recognized to be as effective as castration. The primary use of drugs is to maintain breeding soundness for short periods and to lessen prostatic size if obstructive disease exists. Several agents may be antiandrogenic, and each has a different mechanism of action. Relapses occur after cessation of therapy in all cases.

**Diethylstilbestrol** (0.2 to 1.0 mg PO every 2 to 3 days for 3 to 4 weeks) was reported to be an effective treatment for BPH in dogs. Potential side effects include bone marrow suppression, pancytopenia, and squamous metaplasia of the prostate with ductal obstruction and cyst formation.

**Progestins** may be potent antiandrogens that induce a negative feedback effect, inhibit pituitary gonadotropin secretion, and have a direct effect on the prostate. Medroxyprogesterone acetate (3 mg/kg SC given twice at 4-week intervals) has been used to treat BPH by decreasing prostate size in 4 to 6 weeks without adversely affecting semen quality or libido. It has been shown that doses of medroxyprogesterone acetate between 3.0 and 4.8 mg/kg SC did not affect semen quality for 27 weeks after treatment, although there was a reduction in serum T2 concentrations from weeks 5 to 13 after treatment. A similar study showed that neither megestrol acetate (2 mg/kg PO for 7 days) nor medroxyprogesterone acetate (10 mg/kg SC) produced a change in semen quality. However, 20 mg/kg of medroxyprogesterone acetate produced a rapid and significant decrease in spermatozoa motility, morphology, and output. Other progestins (e.g., cyproterone acetate [1.25 to 2.5 mg/kg/day PO for 15 days], delmadinone acetate [1 to 2 mg/kg SC every month],...
chlormadinone acetate [2 mg/kg/day PO for 3 or 4 weeks]) are also indicated for the treatment of BPH. 

Although most of these studies have shown that progestins are effective and do not have detrimental reproductive effects when used at low doses, patients should be monitored for diabetes mellitus and mammary nodules when treatment is prolonged. 

Flutamide inhibits androgen uptake and/or nuclear binding by binding to androgen receptors. 

Finasteride is a commercially available synthetic steroid that inhibits type II 5α-reductase, which prevents conversion of T₂ into DHT. 

Beagles with BPH that were treated with finasteride (1 mg/kg/day PO for 16 to 21 weeks) showed prostatic atrophy and a 50% to 70% reduction in prostatic volume. This dose of finasteride also decreased serum concentrations of DHT with no adverse effect on testis histology or semen quality. There was a decrease in the third fraction of the ejaculate, but fertility was conserved (matings 20 to 22 weeks after treatment were fertile). A dose–response study of finasteride at 0.1, 0.25, or 0.5 mg/kg/day PO for 7 days in three normal intact male dogs showed significant decreases in serum concentrations of DHT without changing serum concentrations of T₂; therefore, libido and spermatogenesis remained normal. This study suggested that these lower doses may be effective. In a recent study to determine the effect of finasteride at 0.1 to 0.5 mg/kg/day PO in nine client-owned dogs with spontaneous BPH, treatment decreased prostatic diameter, volume, and serum concentrations of DHT after 16 weeks. Finasteride treatment caused a decrease in semen volume but had no adverse effect on semen quality and no effect on serum concentration of T₂. 

Five of nine dogs in this study were used to breed bitches. They had a normal libido during copulation and were successfully bred to bitches that became pregnant.

Finasteride is indicated at a dose of 0.1 mg/kg/day PO, and no adverse effects have been noted after prolonged treatment. Because finasteride does not act quickly, 2 to 3 months of treatment may be required to significantly decrease prostatic size. Finasteride can be combined with a single dose of a long-acting progestin at the beginning of the treatment.

Tamoxifen is a synthetic nonsteroidal antiestrogenic drug with both antagonist and agonist effects. In dogs, tamoxifen produces an estrogenic response. There are insufficient data available about the efficacy of tamoxifen in the treatment of canine BPH.

**PROSTATIC CYSTS**

Prostatic cysts may be associated with BPH and fluid retention caused by obstruction of canaliculi. Cysts are cavitating lesions containing clear to turbid fluid within (retention) or outside (paraprostatic) the prostatic parenchyma. The remnant of the uterus masculinus occasionally results in enlarged cysts that are associated with the prostate by a stalk or adhesions. The cysts can be extremely large and can be palpated from the abdomen, usually displacing the bladder cranially and ventrally. Affected dogs may be asymptomatic or may develop signs referable to concurrent BPH or to physical displacement of abdominal viscera. Radiography reveals a circular fluid density in the caudal abdomen, and ultrasonography can be used to confirm the structure. Cysts can be secondarily infected; surgical excision or omentectomy is the treatment of choice.

**SQUAMOUS METAPLASIA**

Excessive serum estrogen concentrations cause the epithelial cells of the prostate to undergo squamous metaplasia and to decrease secretion of prostatic fluids. The syndrome can occur as a result of exogenous estrogen administration or estrogen-secreting Sertoli cell tumors. Clinical signs are minimal except for potential hemorrhagic urethral discharge and a hyperestrogenic skin pattern. Retention cysts may develop as a consequence of the dilation of prostatic acini secondary to estrogen-induced squamous metaplasia. Rectal palpation reveals an enlarged gland without concomitant signs unless cysts are present. Cytology of prostatic fluids reveals squamous epithelial cells and possible hemorrhage. Preputial swabs can also show evidence of estrogen-secreting tumors by revealing squamous cells like those of a bitch in estrus. Biopsy confirms metaplasia, and treatment is focused on the elimination of the estrogenic source (i.e., castration of the neoplastic testis or interruption of the exogenous estrogen administration). After removal of the estrogen source, the prostate returns to normal.

**PROSTATIC NEOPLASIA**

Prostatic malignancy is uncommon; adenocarcinoma is the most common tumor followed by locally invasive transitional cell carcinomas. Other prostatic tumors, representing less than 10% of all neoplasms, include adenomas, leiomyomas, fibromas, and sarcomas. Adenocarcinomas most commonly appear in 8- to 10-year-old dogs. The prevalence of adenocarcinoma in dogs castrated at a young age is at least equal to (and may be greater than) that in intact dogs. Five histologic grades of adenocarcinoma have been described, and neutered dogs are most likely to have poorly differentiated ones. Concomitant prostatic hyperplasia usually occurs with adenocarcinoma in intact dogs.
Clinical Signs and Diagnosis
Anorexia, weight loss, tenesmus, dyschezia, hematuria, stranguria, and rear limb weakness are common signs in dogs with prostatic adenocarcinoma. This tumor has a great potential for secondary spread to pelvic lymph nodes, lumbar vertebrae, pelvic bones, and more distant sites. The initial clinical manifestations of malignancy include bone metastasis leading to myelopathy, pain, neurologic deficits of the hind limbs, and lameness. Rectal examination reveals an irregular, indurated, immobile, asymmetric, enlarged prostate that may be painful. The prostate may be so enlarged that it may drop over the pelvic brim and create a palpable mass in the caudal abdomen. It is important to consider that the prostate gland should not be detectable in castrated dogs, and the finding of a “normal prostate” is suggestive of malignancy.

In contrast to prostatic adenocarcinoma in men, canine prostatic adenocarcinoma does not appear to be androgen responsive as androgen deprivation has not been beneficial in its management. Tumors do not respond to hormonal therapy or commonly used cytotoxic drugs. Chemotherapy should be used only as a last resort for diffuse metastatic disease. Conversely, a study found that a high grade of prostate intraepithelial neoplasia (PIN; a known precursor of human prostate cancer) is frequently present in the prostates of elderly intact dogs. Its appearance is influenced by testicular androgens as it does not appear in castrated animals.

Canine PIN is similar in its morphology and immunophenotype to its human counterpart and is, therefore, suggested to be a precursor to adenocarcinoma in dogs as well.

Radiographic findings in dogs with prostatic adenocarcinoma include prostatic enlargement and mineralization, sublumbar lymphadenopathy, and lung and appendicular skeletal metastasis. Ultrasonographic appearance of the neoplastic canine prostate includes prostatomegaly, mineralization of the parenchyma, presence of focal to diffuse hyperechoic areas, and an irregular/discontinuous prostatic contour. Exfoliative cytology by transrectal or transabdominal aspiration or needle core biopsy is a successful method for diagnosing prostatic adenocarcinoma. Retrograde urethrocystography reveals periurethral asymmetry as well as narrowing, distortion, or destruction of the prostatic urethra.

Treatment
Intact dogs may benefit from surgical or pharmacologic castration as regression of the hyperplastic component can result in relief. External beam radiation therapy is reported to shrink some canine prostatic tumors.
with relief of urinary outflow obstruction and obstipation, but survival times remain short.\textsuperscript{55} Intraoperative radiotherapy is also a promising new technique for treating localized prostatic carcinoma, having low morbidity and a 30% likelihood of tumor control.\textsuperscript{51} The prognosis is grave. Total transurethral prostatectomy is indicated for early-stage lesions; however, this procedure is technically difficult and most dogs become incontinent after surgery. Surgical resection is not recommended as the disease is not usually diagnosed at an early stage.

**PROSTATIC MARKERS**

Canine prostate-specific arginine esterase (CPSE), the major secretory product of the canine prostate that constitutes more than 90% of canine seminal proteins,\textsuperscript{58} is a known marker for canine prostatic secretion, although its exact role in the various diseases of the canine prostate is not yet completely understood.\textsuperscript{59} CPSE is present in similar concentrations in all fractions of the split canine ejaculate.\textsuperscript{58-60} It is produced under androgenic control and can be inhibited by antiandrogen treatment or surgical castration.\textsuperscript{61-63} (Unfortunately, a CPSE kit is not currently available in the veterinary market.) In one study, serum CPSE was elevated in dogs with BPH (mean concentration, 189.7 ng/ml; \( n = 25 \)) compared with normal intact dogs (mean concentration, 41.8 ng/ml; \( n = 20 \)).\textsuperscript{64} Furthermore, CPSE ranged from 20 to 300 \( \mu \)g/ml in urine samples of normal dogs, and dogs with acute (1000 to 2000 \( \mu \)g/ml) or necrotizing (5 to 10 \( \mu \)g/ml) prostatitis could be differentiated.\textsuperscript{65}

Serum concentrations of prostatic acid phosphatase (AcP) and prostate-specific antigen (PSA) are tumor markers routinely used to monitor recurrence of prostatic carcinoma in men. Information about the usefulness of these markers in dogs is still controversial. According to some studies, prostatic AcP does not seem to be specific and PSA does not increase in dogs with prostatic carcinoma.\textsuperscript{64,66} Although quite similar biochemically to the human enzyme, canine prostatic AcP is approximately 100 times less concentrated in prostatic tissue and plasma than its counterpart in humans.\textsuperscript{67,68}

In one study, serum and seminal plasma concentrations or activities of AcP, PSA, and CPSE were measured in normal dogs, dogs with BPH, dogs with bacterial prostatitis, and dogs with prostatic carcinoma to determine whether these assays would be valuable in differentiating dogs with prostatic carcinoma from normal dogs and those with other prostatic disorders.\textsuperscript{64} PSA was not detected in canine serum or seminal plasma. Serum and seminal AcP activities did not differ significantly between normal dogs and those with prostatic diseases or among dogs with different prostatic disorders. However, serum CPSE activities were significantly higher in dogs with BPH than in normal dogs; mean serum activity in dogs with BPH, bacterial prostatitis, and prostatic carcinoma did not differ significantly.\textsuperscript{64} Canine prostatic adenocarcinoma does not appear to be associated with significant increases in CPSE, AcP, or PSA activities, possibly because of down-regulation of these enzymes by prostatic carcinoma cells.\textsuperscript{64,66} Conversely, another study concluded that low serum total AcP and prostatic AcP do not rule out prostatic adenocarcinoma but an elevated concentration can be a useful criterion for diagnosing canine prostatic cancer.\textsuperscript{69}

**DISCUSSION**

Diagnosing each prostatic disease is difficult because similar signs are observed in dogs with different types of disease. The etiopathology of BPH, the most common prostatic disease in dogs, appears to be associated with a complex mechanism of hormonal imbalances that is not completely understood. BPH is found in a few species (e.g., humans, dogs, chimpanzees).\textsuperscript{68} Considerable information about canine BPH has been learned because dogs are the most practical and reliable model for studying the disease in men.\textsuperscript{70} When interpreting reports, however, anatomic, histologic, and pathologic differences between species should be considered. A complete understanding of the hormonal background of BPH will greatly improve treatment of this disorder. Although it is known that signs of BPH respond to castration or finasteride treatment, more information about 5\( \alpha \)-reductase inhibitors is necessary before they can be widely recommended for treating BPH.

Prostatic carcinoma in dogs is often difficult to diagnose in the early stages of the disease and is even more difficult to manage after a diagnosis is made. A high grade of PIN seems to be an intermediate stage between benign epithelium and invasive carcinoma. Neither prostatectomy nor castration has been found to provide a good quality of life or effectively cure the disease. The lack of hormone dependency may be due to the fact that most carcinomas are diagnosed as end-stage cancer in dogs.

Ultrasonography provides an accurate, noninvasive, diagnostic technique for evaluating the internal architecture of the different diseases of the prostate, although definitive diagnosis should be based on histologic findings.

Serum and seminal prostatic-specific markers could enhance early noninvasive diagnosis of prostatic disease and assessment of treatment response.\textsuperscript{71} CPSE, the major secretory product of the prostate, is regulated by
T2 control and therefore may also serve as a functional marker of the androgenic state and response to antiandrogenic therapy. Results show that proteins of prostatic origin appear in the serum of dogs as a result of prostatic pathology, especially BPH. More studies are needed to confirm the status of AcP as a marker of prostatic cancer in dogs. Canine prostatic adenocarcinoma does not appear to be associated with significant increases in CPSE or AcP activities.

Although further research is necessary to define the exact role of CPSE, it seems to be a promising diagnostic tool for nonneoplastic canine prostatic disorders. Future studies should also address the quantitative relationship among serum and prostatic androgen levels, prostatic androgen-dependent problems, and how these are affected by antiandrogen treatment.

REFERENCES
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1. The prostate is physiologically ____________ organ.
   a. an estrogen-dependent  
   b. an androgen-dependent  
   c. a progesterone-dependent  
   d. a hormone-independent

2. The most common prostatic disease is
   a. squamous metaplasia.  
   b. BPH.  
   c. adenocarcinoma.  
   d. prostatic cysts.

3. As male dogs age,
   a. estrogen and androgen tend to increase.  
   b. androgen tends to increase and estrogen tends to decrease.  
   c. androgen tends to decrease and estrogen tends to stay the same.  
   d. estrogen decreases and androgen remains the same.

4. A common sign of BPH is
   a. dysuria.  
   b. purulent prepuce discharge.  
   c. bloody prepuce discharge.  
   d. hematochezia.

5. The best treatment for BPH is
   a. estrogen.  
   b. castration.  
   c. prostatectomy.  
   d. detailed follow-up.

6. Finasteride is
   a. an androgen-receptor blocker.  
   b. an antiestrogen.  
   c. a 5α-reductase inhibitor.  
   d. an aromatase inhibitor.

7. Squamous metaplasia is related to
   a. excessive androgens.  
   b. exogenous progestins.  
   c. excessive estrogens.  
   d. diminished estrogens.

8. The most common prostatic neoplasia is
   a. adenocarcinoma.  
   b. transitional cell carcinoma.  
   c. adenoma.  
   d. leiomyoma.

9. The major secretory product of the canine prostate is
   a. CPSE.  
   b. prostatic AcP.  
   c. PSA.  
   d. alkaline phosphatase.

10. Definitive diagnosis of prostatic diseases is obtained by means of
    a. radiography.  
    b. ultrasonography.  
    c. exfoliative cytology.  
    d. needle core biopsy.