University of Veterinary Medicine Budapest

Department and Clinic of Reproduction

Literature review of estrogen-related disorders of the male dog

By David Hofmeister

Supervisor: Dr. Farkas Szilvia

Clinical Veterinarian, Assistant Professor

1. Abstracts

1.1 English Abstract

Estrogen and its derivatives play a vital role in both female and male dogs alike, estrogen misbalance as such can manifest in multiple ways within the body and subsequently cause disturbances thus exhibiting a variety of clinic symptoms. Due to the disruption of the homeostasis of these hormones, it may result in systemic illnesses, dermatological changes, significant behavioral changes as well as the development of female like traits in the male dog. Therefore, this thesis will review an array of different literatures, and dive into multiple potential causes that could lead to estrogen related disorders in the male dog, and why this phenomenon occurs. Some disorders that cause this phenomenon include but are not limited to adrenal gland pathologies as well as a variety of testicular tumors. Therefore, this paper will uncover the clinical symptoms observed, diagnostic and treatment methods available and finally review individual case studies in hopes to give a better understanding of estrogen related disorders to both veterinarians and owners alike.

1.2 Hungarian Abstract

Az ösztrogén és származékai létfontosságú szerepet játszanak mind a szuka, mind a kan kutyákban. Az ösztrogén szint eltolódása, mint olyan, többféleképpen megnyilvánulhat a szervezeten belül, szerepet játszhat különféle kórképek kialakulásában, melyek változatos klinikai tünetekkel járhatnak. A hormonális egyensúly felbomlása szisztémás betegségek, bőrgyógyászati elváltozások, jelentős viselkedésbeli változások, valamint a szukákra jellemző tulajdonságok kialakulását eredményezheti a kan kutyában. A kórképek hátterében többek között, de nem kizárólagosan, a mellékvese elváltozásai, valamint különféle heredaganatok állhatnak. Ezért ez a diplomamunka az ösztrogén szint változásával kapcsolatos kórképek irodalmát tekinti át, vizsgálva azon okokat, összefüggéseket, melyek az ösztrogénnel kapcsolatos rendellenességekhez vezethetnek elsősorban kan kutyákban, valamint összefoglalja a megfigyelt klinikai tüneteket, a rendelkezésre álló diagnosztikai és kezelési módszereket, és végül áttekinti az egyes esettanulmányokat, abban a reményben, hogy az állatorvosok és a tulajdonosok jobban megértsék az ösztrogénnel kapcsolatos rendellenességeket.

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List of abbreviations

ACTH - Adrenocorticotropic Hormone

ADH – Adreno-Dependent Hyperadrenocorticism

AFP – Alpha - Fetoprotein

CBC – Complete Blood Count

CD30 - TNF receptor superfamily member 8

CEUS – Contrast Enhanced Ultrasonography

c-KIT - Proto-oncogene c-KIT

CT - Computed Tomography

E1 – Estrone

E2 – Estradiol

E3 – Estriol

E4 – Esterol

HAC – Hyperadrenocorticism

IHC – Immunohistochemistry

INH-α – Inhibin A

LDDST – Low Dose Dexamethasone test

MAO-B - Monoamine Oxidase B

OCT3/4 - Octamer Binding Transcription Factor

-OH – Hydroxyl

PDH – Pituitary-Dependent Hyperadrenocorticism

PLAP – Placental Alkaline Phosphatase

SCT – Sertoli Cell Tumors

TFS – Testicular Feminization Syndrome

2. Introduction

Estrogen-related disorders in male dogs have been a subject of interest for many years. These disorders can give rise to significant health issues and have a profound impact on the overall well-being of afflicted animals. In this comprehensive literature review, we delve into the current state of knowledge regarding estrogen-related disorders in male dogs.

Estrogen-related disorders in male dogs hold significant importance for both the well-being of the animals and the field of veterinary medicine and science. These conditions can result in a range of health issues, making early diagnosis and intervention critical. Identifying and treating disorders these disorders can aid in improvement of a dog's quality of life [1]. Furthermore, recognizing these disorders is essential for responsible breeding practices, as affected males may not be suitable for breeding [2]. Studying these disorders contributes to our understanding of canine reproductive and endocrine biology, benefiting both veterinarians and researchers, therefore expanding the world of veterinary medicine.

In practical terms, raising awareness about estrogen-related disorders is vital for dog owners, ensuring they recognize the signs, thus, seek veterinary care. By doing so, they can help their dogs receive timely and effective treatment, ultimately leading to better outcomes. Overall, the importance of addressing estrogen-related disorders in male dogs lies in the well-being of the animals, advancements in veterinary science, responsible breeding practices, and informed pet ownership [2].

The most important estrogen-related disorders in male dogs are induced by testicular diseases such as Sertoli cell tumors (SCT). SCTs produce excess estradiol, causing clinical signs such as gynecomastia and decreased libido [3]. Rarely, testicular intersex or hermaphroditism can lead to estrogen production from ovarian tissue in male dogs [4]. Adrenal tumors are another potential source of elevated estrogen levels [5]. Additionally, exposure to estrogen-containing medications or environmental sources of estrogen can disrupt hormonal balance. Liver disease may hinder the breakdown and removal of hormones, contributing to hyperestrogenism [6]. Various endocrine disorders can also play a role in this hormonal imbalance [3]. As such all these diseases factor into the potential disruption of estrogen levels within the male dog and therefore pose a high level of importance in veterinary medicine.

3. Objectives

This work aims to

a) Raise awareness about estrogen related disorders in male dogs to owners and veterinarians.
b) Review pathogenesis of disorders that affect the estrogen balance within male dogs, and what clinical symptoms to be aware of and how to effectively manage, diagnose and treat such cases.

4. Materials and Methods

Literature Data was obtained from various sources such as Google Scholar (https://scholar.google.com), PubMed (https://pubmed.ncbi.nlm.nih.gov), ScienceDirect (https://www.sciencedirect.com) and Wiley Online Library (https://onlinelibrary.wiley.com) using predefined search criteria. The selection of articles was determined by adhering to pre-established inclusion and exclusion criteria, with a keen emphasis on assessing their quality and alignment with the desired objectives. Scientific Handbooks were also checked for conformation and data. Furthermore, the library of the University of Veterinary Medicine Budapest (Hutÿra Ferenc Library, Archives and Museum) was included in the research.

5. Physiology of Estrogen

Estrogen is a crucial sex hormone in female dogs (bitches), as it regulates the estrous cycle, prepares the reproductive system for mating and pregnancy, and influences behavioral and physiological changes at different stages of the cycle. In male dogs, estrogen is present in smaller amounts, primarily produced through the conversion of testosterone, and plays a minor role in maintaining overall health, particularly in bone density. Therefore their imbalance can lead to multiple disorders [1, 2].

Estrogens encompass a group of hormones, with four primary structures: Estrone (E1), Estradiol (E2), Estriol (E3), and Esetrol (E4). These structures vary based on the number of hydroxyl (-OH) groups attached to them, leading to corresponding abbreviations, such as Estrone (E1), characterized by a single -OH group. **Figure 1** [9]**.**

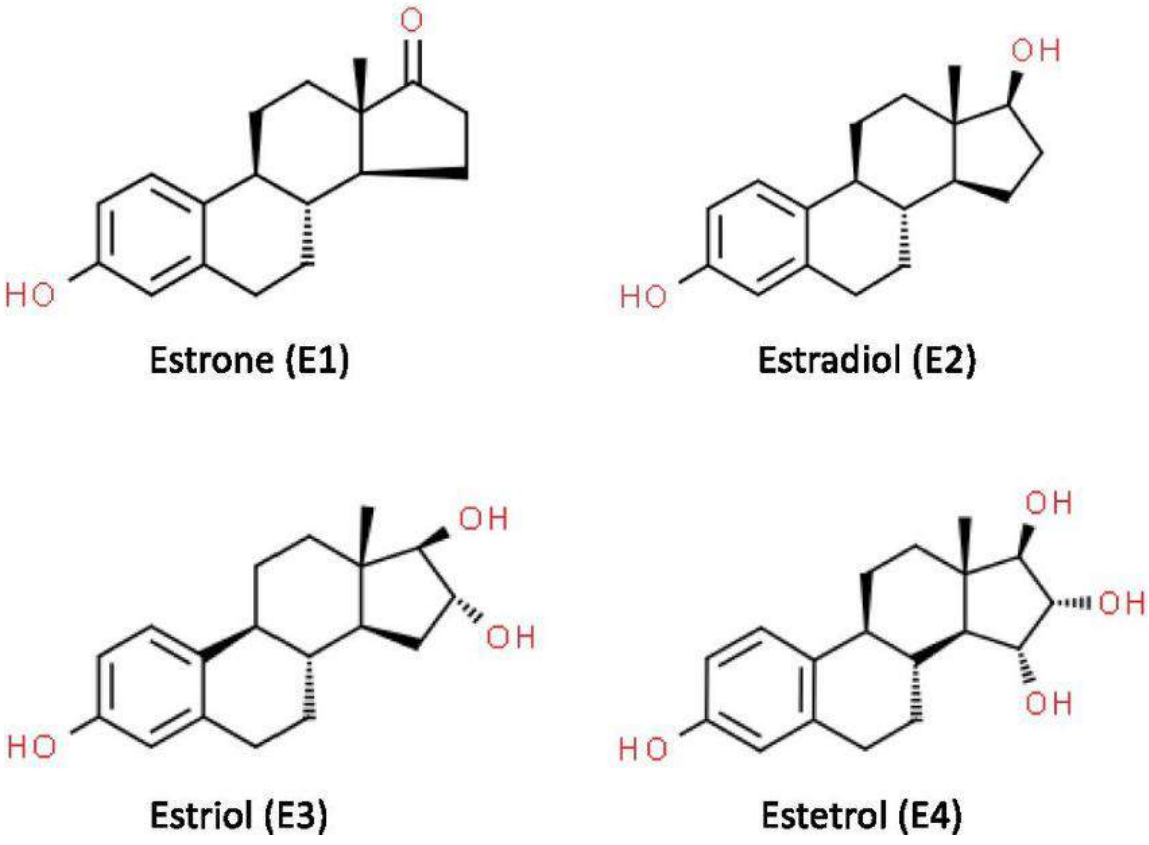

Figure 1 – Skeletal structure of E1, E2, E3 and E4 [9].

In dogs, the synthesis of E1 involves several steps, starting with the conversion of cholesterol, which is produced in the liver and gastrointestinal tract. Cholesterol is converted into pregnenolone and further to progesterone [10]. From progesterone, the process continues with the conversion of progesterone into androstenedione, which is an androgen. Androstenedione, a precursor, is ultimately transformed into E1, one of the primary forms of estrogen [11]. While the ovaries, especially in females, are the primary source of estrogen production, including the more potent E2. E1 can also be synthesized in smaller quantities in peripheral tissues like fat cells, skin, and muscle[12]. This synthesis is regulated by hormonal control systems and is crucial for the estrous cycle and overall health in dogs. These hormones are synthesized in the female and the male body although representing a far greater importance in female dogs [12]**. Figure 2** briefly displays this cycle [13].

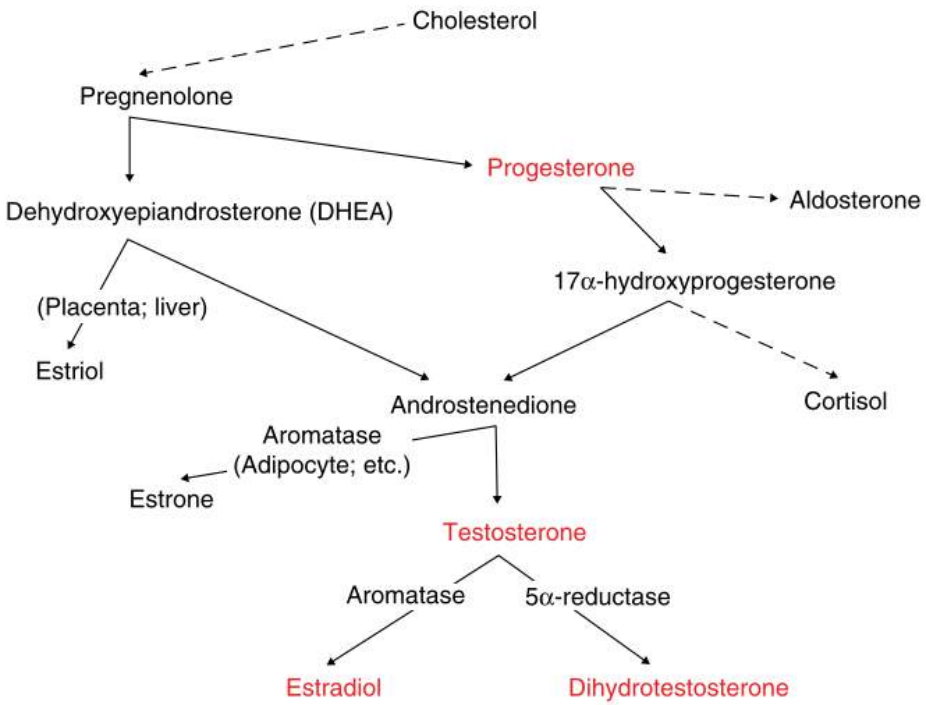

Figure 2 – Summary of estrogen synthesis [13]

In male dogs, estrogen and its derivatives are typically produced in smaller quantities compared to females. The primary source of estrogen in male dogs is the testes, where some estrogen is produced as a byproduct of testosterone synthesis [14]. Testosterone is the primary sex hormone in males, and it is synthesized in the Leydig cells of the testes. The conversion of testosterone into estrogen, specifically E2, is facilitated by the enzyme aromatase, which can be found in various tissues, including the testes. This conversion of testosterone to estrogen occurs in small amounts in males and is generally not a primary source of estrogen in their bodies. Some peripheral tissues in male dogs may also have the capacity to convert androgens (male hormones like testosterone) into estrogens, but the levels are typically much lower than those found in females[6–9]

E1's function in male dogs is primarily associated with maintaining secondary sexual characteristics. It indirectly influences bone health by contributing to bone density and strength, which is important for overall health. However, its presence in males is typically minimal compared to females [8].

E2 in male dogs plays a limited role as well, nonetheless it supports bone health by maintaining bone density and strength. While it is present in small amounts in males, its influence on male reproductive behavior is generally indirect. In female dogs, E2 is pivotal for regulating the estrous cycle, fertility, and the development of secondary sexual characteristics [16], but in males, its functions are minor in comparison to testosterone's central role in male physiology and behavior [17]. In males, E3 and E4 are produced in very small amounts, and their functions are not well-documented or as prominent as those of other hormones, such as testosterone. Therefore, the specific functions of E3 and E4 in male dogs are not well-defined, and they are not considered a significant hormone in male physiology [12].

6. Adrenal gland disorders

The adrenal glands, which are found cranial to the kidneys, are part of the endocrine system, and are responsible for the production of multiple different hormones, all of which have a range of functions within the body. The outer region, or adrenal cortex, produces cortisol, this aids in regulation of metabolism, blood glucose levels, control of inflammatory mediators, and aldosterone, which manages electrolyte levels and blood pressure. The inner section, or adrenal medulla, synthesizes adrenaline and norepinephrine. These hormones initiate the "fight or flight" response and are activated in response to stress, as well as an elevated heart rate or blood pressure. Adrenal glands also secrete small amounts of sex hormones, thereby contributing to secondary sexual characteristics in dogs. Moreover, they help control the immune system and play an important role to help the animal respond to stressful situations according, this allows for a balanced response to various physiological and environmental demands [18].

Adrenal disorders may result in abnormal hormone production or further disruptions, which can affect the role of the adrenal glands within the body. Commonly occurring disorders in dogs related to the adrenal glands include hyperadrenocorticism, the overproduction of cortisol, or hypoadrenocorticism, the underproduction of cortisol [19].

6.1 Pathogenesis

There are two main types of hyperadrenocorticism (HAC): pituitary-dependent hyperadrenocorticism (PDH) versus adrenal-dependent hyperadrenocorticism (ADH). About 85 per cent of all cases are related to the disorder called PGPHD where the pituitary tumor causes excess secretion by the adrenal cortex. This means that ADH is due to benign or malignant tumor with excessive production of cortisol in the adrenal glands. They may as well lead to a rise in the level of cortisol as well as male and female hormones [20, 21].

HAC secondary to sex steroid excess is one kind of a Cushing's syndrome that is caused by an adrenal/pituitary tumor whose symptoms include among others the hair loss, disordered sexual functions, and hepatopathy. Additionally, some breeds, such as miniature poodles and Chow chows, have atypical HAC which could be due to adrenal tumors instead of Pituitary dependence. However, diagnosis is often difficult and requires hormonal testing, imaging, and biopsy. The treatment involves medical management, adrenalectomy of the tumor or radiation therapy. [21, 22].

6.2 Diagnosis

The diagnosis of HAC can be challenging and usually requires differentiation to be done between PDH and adrenal-dependent disease. Various tests can be used for diagnosis, including the low-dose dexamethasone suppression test (LDDST) [23], which is a method used to assess adrenal gland function and aids in diagnosis of different hormonal disorders, in particular those involving cortisol regulation, such as Cushing's syndrome. During the LDDST, a low dose of a synthetic glucocorticoid known as dexamethasone is given to the patient, prior to administration, a measurement of cortisol levels in the patient's blood needs to be done as well as after the administration of the dexamethasone. In a healthy dog, dexamethasone will suppress cortisol production, resulting in lower post-dexamethasone cortisol levels. However, if cortisol levels remain elevated after dexamethasone administration, this could indicate a potential abnormality in cortisol regulation, which is often seen in conditions like Cushing's syndrome. Therefore, the LDDST is an important diagnostic tool for establishing if a patient does indeed have Cushing's disease and can subsequently be used in further diagnostic procedures [23].

An additional test that can be done is the adrenocorticotropic hormone (ACTH) stimulation test, also known as the cosyntropin stimulation test. This test is used to evaluate the function of the adrenal glands and also diagnose hormonal disorders related to cortisol regulation, such as Addison's disease [24]. During this test, a synthetic form of ACTH is administered to the patient, typically via intravenous injection. Once again blood samples are collected before and then at specific time intervals after the injection to measure cortisol levels and how they may change. In a healthy dog, cortisol levels should elevate in response to cosyntropin. The test allows veterinarians to differentiate between primary and secondary adrenal insufficiency by assessing the adrenal gland's ability to produce cortisol. An altered cortisol response to the test can suggest adrenal dysfunction, while an appropriate response may be normal, it may also indicate secondary adrenal insufficiency and thus the need for further diagnostic methods. Therefore, the ACTH stimulation test is a valuable diagnostic tool for evaluating adrenal function and determining the underlying cause of cortisol-related disorders. Adequate interpretation of the test results is necessary, and based on this, additional tests may be required to confirm the diagnosis and further aid in establishing treatment options. In addition, a measurement of steroid precursors may also be warranted, this includes measuring endogenous plasma ACTH concentrations to differentiate between PDH and adrenal tumors. Diagnostic imaging techniques such as

abdominal radiography, ultrasonography, or Computed Tomography (CT) can also be used to visualize the pituitary and adrenal glands. Overall, a combination of clinical evaluation, laboratory tests, and imaging techniques is necessary for the accurate diagnosis of HAC in dogs [24–26].

6.3 Symptoms and treatment

HAC is a hormonal disorder in dogs; therefore, it can present with a range of different symptoms, whereby in certain cases, dogs with HAC may have abnormal levels of sex steroids. This can lead to different dermatological manifestations such as alopecia, thin skin, and hyperpigmentation. Non dermatological signs of HAC may include perianal adenoma, behavioral estrus, and prostatomegaly. Serum blood abnormalities that are associated with HAC include elevated levels of serum alkaline phosphatase and alanine transferase, hypercholesterolemia, hyperglycemia, and decreased blood urea nitrogen [25, 27]. The cytological results if collected from the affected male dog from the preputium can resemble similar cytological characteristics to that of the female dog in the case of high estrogen levels.

Furthermore, dogs with adrenal sex hormone induced alopecia following mitotane treatment may develop a mineralized mass in the adrenal glands, and imaging techniques such as abdominal radiographs, ultrasonography, computed tomography, or magnetic resonance imaging can be used to identify adrenal tumors and associated disorders induced by the mitotane treatment [28]. Treatment options for canine HAC include medical, surgical, and radiation therapy, with mitotane being the most successful medical treatment option. Ketoconazole is another steroid inhibitor used to treat HAC, but it is not often used due to expense and potential side effects [29]. Deprenyl, a Monoamine oxidase B (MAO-B) inhibitor may also be used to treat PDH, but its efficacy compared to the placebo is unknown [30].

In summary the treatment options for dogs with HAC include medical management with drugs such as mitotane or trilostane, surgical adrenalectomy, radiation therapy, and medical management with glucocorticoids. Surgical adrenalectomy is effective but may have complications, while radiation therapy is expensive and time-consuming it does consequently have less side effects. Medical management with glucocorticoids is necessary during surgery and afterward to prevent cortisol withdrawal syndrome [31].

6.4 Case studies

An 11-year-old Labrador Retriever was referred to a veterinary hospital for evaluation of suspected hyperadrenocorticism. The clinical signs that were noted by the examining veterinarian included polyphagia, polydipsia, and polyuria. Abnormalities that were seen during the physical examination were a rough coat and a sagging abdomen. Results of a CBC (complete blood count) revealed mild lymphopenia, and serum biochemical abnormalities included moderately high alkaline phosphatase activity. Repeated noninvasive measurements of blood pressure were within normal parameters. Abdominal radiography showed a mineralized mass cranial to the left kidney, and ultrasound examination confirmed that the mass originated from the region of the left adrenal gland. A low dose dexamethasone suppression test showed suppression of cortisol at the 8-hour mark but not at 4-hour mark following injection. Endogenous ACTH concentration was low. Validation of sex hormone assays for dogs with adrenal tumors showed elevated concentrations of estradiol, progesterone, and 17-hydroxyprogesterone. Treatment with mitotane and prednisone was initiated for two dogs with hyperadrenocorticism and excessive sex hormone production by an adrenal tumor. However, no improvement was observed following 10 days of treatment, and an additional radiograph showed an increase in the size of the left adrenal mass. Excessive production of sex hormones by an adrenal tumor caused clinical signs consistent with hyperadrenocorticism. However, cortisol concentrations were low following ACTH administration, suggesting an inhibition of cortisol production by the tumor. Removal of the tumor resolved the clinical signs [32].

7. Testicular tumors

Testicular tumors in dogs encompass several types, including Sertoli cell tumors, Leydig cell tumors, seminomas, teratomas, and mixed tumors. Sertoli cell tumors are common and often benign but can produce excess estrogen, leading to feminization and other symptoms. Leydig cell tumors are usually benign but may produce androgens, resulting in masculinization. Seminomas are generally malignant and can metastasize to other parts of the body. Interstitial cell tumors are typically malignant and are more common in older dogs. Teratomas are rare and can contain various tissue types, both benign and malignant. Mixed tumors consist of different cell types and may have variable behavior. The type of tumor and its potential malignancy influence the treatment and prognosis, with surgical removal of the affected testicle(s) being the primary treatment for most cases [33, 34].

7.1 Sertoli cell tumor

7.1.1 Physiology and Pathogenesis

SCT are neoplasms that arise from the testes, and their prevalence is higher in cryptorchid dogs. A study of 234 cases of SCT in dogs found that most were benign. However, five cases of multiple primary tumors were observed, including two dogs with a seminoma and SCT in opposite testes [35].

Cryptorchidism and testicular neoplasia are associated with a higher incidence of SCT in dogs. SCT is more commonly found in undescended testes, and the right testis is affected more often. Bilateral cryptorchidism is also more common than expected, and the testes are smaller and lie closer to the kidneys [9]. The low superoxide dismutase activity in the cryptorchid testis and low blood plasma inhibin-α concentration of dogs with cryptorchidism may be related to the occurrence and development of tumors in canine cryptorchid testes. The blood plasma concentration of INH-α in cryptorchid dogs is lower than in normal dogs, which may be a risk factor for the occurrence of testicular tumors, especially SCT and therefore abnormal function of SCT cells may induce markedly high INH-α production. Additionally, a high concentration of heat shock protein 70 in the cryptorchid testis may accelerate proliferation of SCT cells [36].

7.1.2 Clinical presentation

Dogs with SCT may experience feminization, which is caused by hyperestrogenism. The signs of feminization include decreased libido, odor, and lethargy. The feminization is due to inhibition of thyrotropic hormone secretion from the anterior pituitary by excessive levels of estrogen. Increased values of estradiol were demonstrated in two of three dogs examined in the study. While this assumption has never been demonstrated continuously, it is presumed due to SCT's ability to naturally produce estrogen. It is reported that testosterone values are comparable in affected and unaffected animals [37].

Furthermore, it may develop into myelotoxicity, which causes the bone marrow's function to become suppressed, and consequently there is reduction in the number of blood cells produced. This syndrome is mostly caused by the tumors' ability to produce and release excess estrogen into the dog's bloodstream. As estrogen is not very abundant in male dogs, elevation of this hormone may have multiple different effects within the body, particularly affecting the bone marrow, and as such resulting in myelotoxicity [38].

Myelotoxicity starts with Sertoli cell tumors that produce excessive estrogen. Hematopoiesis is the term used to describe the normal production of blood cells within the bone marrow and this hormonal imbalance may result in interference with the process thereby causing anemia. Hematopoiesis is a process that involves the development of red blood cells, white blood cells and platelets. This disturbance can have serious implications on the dog's overall health. [8].

As mentioned previously, one of the consequences of myelotoxicity is anemia, which results from the reduced production of red blood cells. The symptoms of anemia include weakness, fatigue, and pale mucous membranes. Reduced leukopoiesis may also contribute to leukopenia. A decreased white blood cell count weakens the immune system's ability to defend against infections, making the dog more susceptible to illnesses. Finally, reduced thrombopoiesis, the production of platelets, can result in thrombocytopenia, which is characterized by fewer platelets. Platelets are important in the coagulation cascade, so a decrease in their number can lead to bleeding and clotting disorders [8].

However, it should be pointed out that some Sertoli cell tumors do not cause any myelotoxicity at all, while others may result in various grades of myelotoxicity in different patients or individual cases. Myelotoxicity is based on the size of the tumor, the extent of hormone production, and the general variability between dogs. The presence of

hematological myelotoxicity will depend on individual cases; however, some affected dogs might never present myelotoxic manifestations. [39].

7.1.3 Diagnosis

Signs of Sertoli cell tumours in male dog are often diverse. The most common symptoms comprise skin-related problems which include symmetrical alopecia, increased pigmentation, and thickened areas of skin. In most cases, these cutaneous alterations are usually accompanied by gynecomastia and a loose prepuce which are female attributes. Apart from that, male dogs with Sertoli cell tumours can have a testicular mass, decreased function in the other testicle, lower sperm production and prostatomegaly.[39].

Ultrasound is a diagnostic imaging technique that uses high-frequency sound waves to demonstrate images of the internal structures of the body. In the context of detecting testicular tumors, ultrasound can be used to visualize the testicles and identify any abnormal growths or lesions. Different ultrasound techniques can be used to characterize testicular tumor lesions in the dog. These include B-mode ultrasound, color and spectral Doppler vascular ultrasonography, power Doppler, B-flow, and contrast-enhanced ultrasound (CEUS) [40]. B-mode ultrasound provides a two-dimensional image of the testicle and allows for comparison of the lesions to be made with the normal surrounding structure of the testicular parenchyma. Doppler ultrasound measures blood flow within the testicular tissue and can help evaluate the vascularity of the lesions if present. Power Doppler and B-flow imaging provide color mapping of the blood flow within the lesion itself. CEUS on the other hand involves the injection of a contrast agent to enhance the visibility of the blood vessels. By using these ultrasound techniques together, veterinarians can assess the size, location, and vascularity of testicular tumor lesions in dogs. This information can therefore aid in the diagnosis and classification of tumors, as well as in determining the best course of treatment. A benefit of this is that, ultrasound is a non-invasive and safe procedure that can provide important information for the management of testicular tumors in dogs [40].

An important thing to lookout for when dealing with SCTs is the development of metastasis in other areas of the body. This is due to the fact that, malignant Sertoli cell tumors has the potential to invade nearby structures, such as blood vessels and lymph vessels, thus facilitating the spread of metastatic cells to other areas.

Metastasis of malignant Sertoli cell tumors to local lymph nodes include the inguinal nodes which are in groin areas. However, the metastasis could be spread to other Lymph nodes easily. Additionally, these tumors can metastasize to distant organs like the kidneys[41] or lungs[39], with the lungs being a common site for the secondary tumors to develop. As the cancer cells circulate through the bloodstream or lymphatic system, they can establish new growths in these distant sites, leading to further health complications for the affected dog.

Post surgery is another way of detection that is built on the methods of immuno-histo-chemistry (IHC). Although being used mostly in human medicine, the markers and their effectiveness have been tested in the case of canine testicular tumors. IHC is a laboratory technique used to detect specific proteins in tissue samples. It involves the following steps: preparing and sectioning tissue samples, retrieving antigens, incubating with primary antibodies, using secondary antibodies with markers, visualizing the results, and sometimes counterstaining [42]. IHC is crucial in various fields, helping diagnose diseases and analyze protein expression in tissues, and provides insights into the presence and location of target antigens within cells and tissues[43]. Some canine testicular tumor markers have been studied, however more research is still warranted to achieve accurate diagnosis with the usage of these markers. One study was done to check the specificity of tumor markers such as Placental Alkaline Phosphatase (PLAP), alpha-fetoprotein (AFP), inhibin-alpha, vimentin, OCT3/4, CD30, desmin, and c-KIT in canine seminoma and SCT. c-KIT was found to be the most sensitive marker in canine seminoma cases; However, OCT3/4 was not expressed in any canine seminoma cases. PLAP staining was also used and was detected minimally, although presented to be heterogenous in canine SCTs, with 20% of cases displaying a positive reaction [42].

7.1.4 Treatment and Prognosis

The treatment of Sertoli cell tumors in dogs will usually involve a combination of techniques, such as surgical removal of the tumor as well as any additional medical interventions deemed to be necessary. The specific treatment approach will always depend on the individual dog, extent of the tumor, and any associated complications [15].

The main and most effective treatment option in the case of Sertoli cell tumors in dogs is the surgical removal of the affected testicle, a procedure known as orchiectomy. This surgery is considered curative in most cases as it eliminates the source of excess hormone production and will halt the tumor from spreading. Orchiectomy is a generally

straightforward procedure and is well-tolerated by most dogs, thereby remaining first line of treatment by many veterinarians [44].

Following the removal of the affected testicle, the testicular tissue is typically sent for histopathological examination. This evaluation aids in confirmation or rejection of the diagnosis as it determines the tumor's characteristics, such as the type of tumor as well as whether it is benign or malignant [45].

In certain cases, further medical treatment may be needed. This is due to the fact that Sertoli cell tumors can sometimes be accompanied by other complications, such as myelotoxicity due to the excess hormone production caused by SCTs, which can lead to findings like anemia, leukopenia, or thrombocytopenia. In such cases, medical treatment may include hormone suppression to manage clinical signs related to excess estrogen, as well as supportive care, which could involve blood transfusions or medications counteract the hematological alterations [8, 38].

Regular follow-up examinations and monitoring are advised to monitor the dog's status and ensure there is no recurrence of the tumor or related complications. As such these follow-up visits help the veterinarian track the dog's overall health and recovery, ensuring the best possible outcome.

It's important to note that the prognosis for dogs with Sertoli cell tumors is generally favorable, especially if the tumor is benign and has not yet spread. However, if the tumor is malignant and has spread to other parts of the body, the prognosis may be poor, and additional treatments, such as chemotherapy or radiation therapy, could be considered. The specific treatment plan should be discussed with the owner with the presence of the treating veterinarian who will consider the dog's individual condition, the extent of the tumor, and any potential complications. Early detection and prompt treatment are key to achieving the best possible outcome for dogs with Sertoli cell tumors [35, 46].

8. Leydig cell tumors

8.1 Physiology and pathogenesis

Leydig cells, which are in the interstitial tissue of the testes, are responsible for the production of testosterone. They are stimulated by the luteinizing hormone (LH), that is released from the anterior pituitary gland. LH is released in response to gonadotropin-releasing hormone (GnRH). Leydig cells have specialized LH receptors on their cell membranes, therefore when LH binds, this triggers an enzymatic cascade allowing testosterone synthesis to be initiated. During this process cholesterol is converted into testosterone, after which it is released into the bloodstream, if target levels of testosterone are reached in the blood, a signal is sent to the hypothalamus and pituitary to reduce the release of GnRH and LH, this is known as the negative feedback loop [47–49].

Leydig tumors originate from uncontrolled proliferation of interstitial Leydig cells and are the most commonly found tumors, one study revealing that these tumors occur in about 50% of cases in dogs above 10 years of age [33]. Leydig cells are located between seminiferous tubules, often in groups and close to blood vessels, they have a basal membrane, which separates them from the surrounding stroma [50]. They are characterized by large oval or multiangular cells with rich cytoplasm, multiple fine vacuoles of different sizes and may include erythrocytes filled cysts [46].

Leydig cell tumors in dogs can be benign or rarely appear to be malignant. Occurrence of these tumors is theorized to be dependent on genetic factors, breed predisposition, with specific genetic mutations occurring as well, all which can lead to uncontrollable growth of these cells within the testicles [15].

8.2 Clinical presentation

As mentioned previously Leydig cell tumors typically occur in older intact male dogs, testicular enlargement is one of the most common signs of Leydig cell tumors, the affected testicle becoming notably larger than the unaffected one, typically being painless. However, in some cases dogs may show signs of scrotal pain or discomfort where the dog may lick or bite at their scrotum and exhibit discomfort when the area is palpated or touched. A palpable mass may be detected in the scrotum if the mass is large enough or causes notable swelling [51]. Behavioral changes may be noted as well, this may be due to the production of excess testosterone. These changes are increased aggression, restlessness or mounting behavior [34].

Secondary sexual characteristics can be seen to develop as Leydig cells can produce small amounts of estrogen in addition to the testosterone production [52]. Leydig cells have the capacity to express the enzyme aromatase, which can convert testosterone into estradiol, in Leydig tumors the cells are overactive and therefore produce large amounts of testosterone. This excess ultimately ends up being converted by aromatase into estrogen by the activity within the tumor tissue itself. The estrogen production may be localized to the affected testicle and not have significant systemic effect on serum estrogen concentrations. In the event of increased serum estrogen concentrations, we may see clinical signs. Such signs include but are not limited to changes in behavior, feminization of secondary sexual characteristics with mammary gland enlargement, alopecia and aggression alongside the increased testosterone levels seen with Leydig cell tumors [14, 53–55].

8.3 Diagnosis and treatment

Diagnostic steps of Leydig cell tumors first involves taking a detailed medical history and performing a physical examination of the patient. as mentioned above common clinical signs to look out for are scrotal enlargement, pain or discomfort in the scrotal area and enquiring the owner about any noted behavioral changes in the male dog. They may report things such as changes in appetite, increased thirst and visible coat quality changes [24]

One study used ultrasonography to distinguish between different types of testicular tumors, they did this by analyzing the different vascular patterns present in scrotal tumors with the support of using multiple types of US modes to allow for better differentiation. 27 dogs were included in this study with 14 suffering from leydigomas. The study demonstrated that B-Mode ultrasonography did not provide differentiation between tumor types. Assessment of the pampiniform plexus and testicular arteries was done with color and pulse Doppler. Color doppler was used to classify blood flow of lesions as either absent or present, and if present as peripheral or intralesional. For Leydig cell tumors, ultrasound analysis showed that mostly all were focal lesions, round or oval and ranged from 4 to 30 millimeters. It was observed that leydigomas had a higher proportional of perilesional and/or perilesional/ intralesional blood flow in comparison to other tumors [40]. **Figure 3** [40]**.**

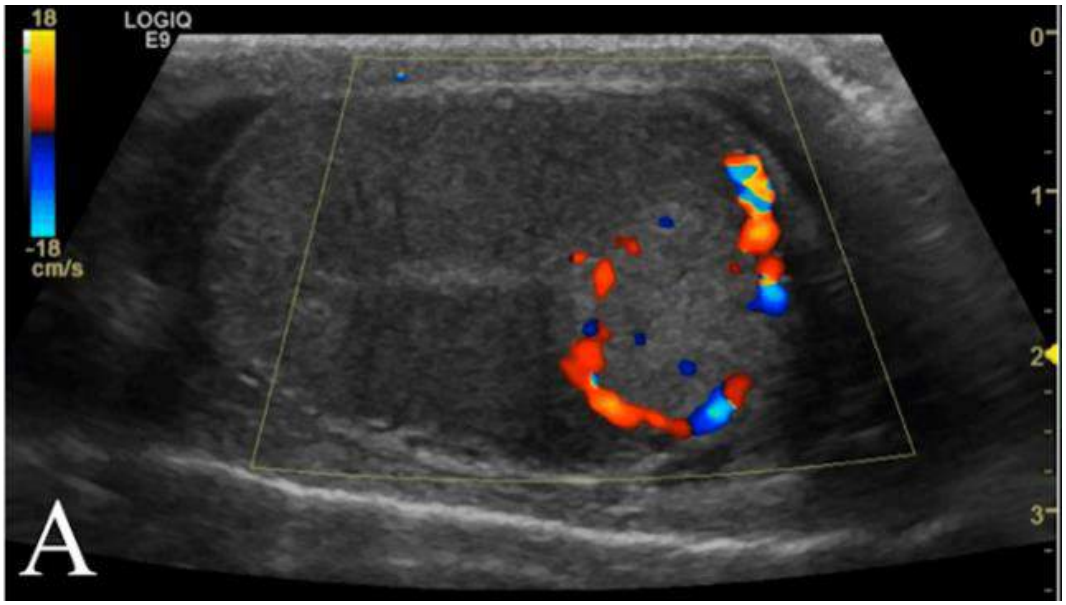

Figure 3 – Doppler Imaging of a Leydig cell tumor [40].

Another study measured the hormone concentrations in peripheral and testicular venous blood in dogs with multiple different testicular tumors and observed a difference in hormone level in comparison to normal dogs. Dogs with Leydig cell tumor also showed an increase in estradiol concentrations in the blood just like in Sertoli cell tumors. This study also demonstrated moderate feminization like signs in affected dogs, atrophy of the unaffected testicle, extreme alopecia and minor gynecomastia. These dogs were also recorded to have less testosterone than normal dogs as estradiol and testosterone share a negative feedback loop. A more dramatic decrease of testosterone was seen if both testicles were affected by Leydig cell tumors, and only these tumors were demonstrated to have bilateral testicular involvement. The amount of estrogen secreted by Leydig cell tumors is said to may be linked with the stimulation of aromatase activity in the remaining Sertoli cells within the testes [14].

Histopathological analysis can be done after removal of the affected testicle(s) or after sample collection for a biopsy [51]. Histopathological findings typically reveal certain characteristic features that aid confirming the diagnosis. One of the features is identification of large, polygonal cells that are arranged in solid sheets or cords and are distinctive in appearance in comparison to normal testicular tissue [56]. Leydig cell tumors may exhibit a vascular network that is more prominent than in surrounding tissues and one of the key distinguishing features is the absence of germ cell elements

(spermatogonia, spermatocytes, and spermatids), therefore these tumors do not contain structures associated with normal sperm production. There may also be the presence of mitotic figures indicating that these cells are undergoing division and further potential tumor growth. In one study the Leydig cell tumor was circumscribed, however showed to be unencapsulated and composed of solid cords, as well as with packets of polygonal cells with eosinophilic cytoplasm. The cells appeared to have a round or oval nucleus with finely stippled chromatin and a prominent central nucleus [56]. **Figure 4** demonstrates the histological features of a Leydig cell tumor [57].

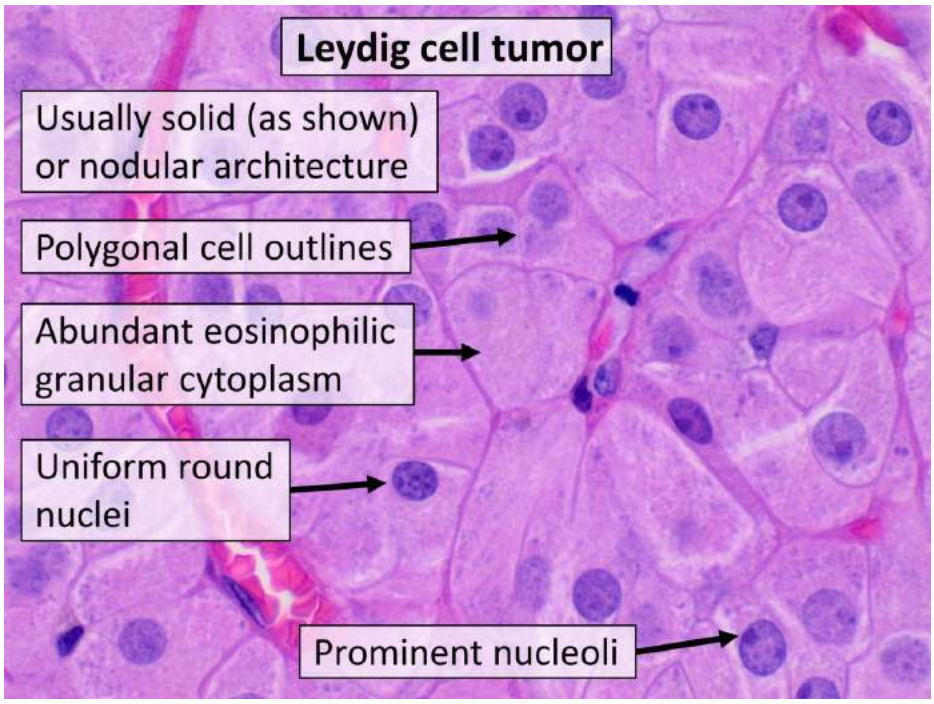

Figure 4 – Histopathological analysis of a leydig cell tumor [57]

Leydig cell tumors are mostly considered to be benign in dogs, although one study showed distant cutaneous metastasis in two dogs. One dog appeared to have unilateral cryptorchidism alongside a rapidly growing cutaneous mass and the second dog demonstrated enlargement of the right testicle with multiple cutaneous nodules. Unfortunately both dogs died a month and a half later following castration [58]. No mention of feminization or estrogen abnormalities were listed in this study, as it was not the primary focus.

Once the tumor is diagnosed, surgical removal is the recommended treatment. In most cases, a unilateral orchiectomy is performed, which involves removing the affected testicle. In some cases, if both testicles are affected, a bilateral orchiectomy may be necessary. The surgery is usually curative if the tumor has not spread. If the Leydig cell tumor is found to be malignant or has spread to other parts of the body, additional treatments, such as chemotherapy, may be recommended. The specific treatment plan will depend on the individual case and the extent of the disease [15].

9. Conclusion

My first (a) aim was to raise awareness to owners and veterinarians regarding estrogen related disorders in the male dogs and what symptoms to be aware of when dealing with this pathology.

To do so I reviewed over two dozen articles to compile a variety of clinical signs to be vigilant about when dealing with estrogen related disorder. Studies demonstrate that non castrated male dogs over the age of 10 are likely to develop tumors of the testicles that are associated with an over production of estrogen. Dogs that do not develop testicular tumors may develop underlying endocrine disorders which could also result in developing hormonal disbalances such as an overproduction of estrogen.

My second aim (b) was to review pathogenesis, symptoms, diagnosis and treatment methods. Pathogenesis mainly revolved around age and the data compiled on uncastrated male dogs and their likelihood of developing disorders related to estrogen disbalances. With respect to symptoms observed, further articles were reviewed where behavioral changes, alopecia, and enlargement of the scrotum were seen to be the leading clinical symptoms. Regarding diagnosis, blood work, ultrasound examinations and histopathological analysis were seen to be the best course of action when diagnosing testicular tumors and endocrine disorders. Finally bilateral castration was always recommended to be the main treatment option as well as removal of metastatic cells or lesions if present.

In conclusion estrogen related disorders in male dogs are commonly occurring in senior dogs and owners should be informed and veterinarians aware of the hormonal disbalance that can occur as a result. Both parties should remain vigilant of the symptoms that can arise and problems that this disease can cause.

10. Summary

Estrogen related disorders in male dogs may occur in uncastrated senior dogs. The main cause of this is the occurrence of testicular tumors, particular attention should be paid to Sertoli cell tumors and Leydig cell tumors. Both tumors may influence the enzyme aromatase, ultimately resulting in the transformation of testosterone into estrogen resulting in the hormonal disbalance that can be seen. This can lead to the development of secondary sexual characteristics and feminization of male dogs, as well as other behavioral alterations and scrotal changes such as enlargement, pain, and swelling may be noted.

Another pathology causing over production of estrogen are adrenal disorders in male dogs. Conditions like adrenal gland tumors or hyperplasia (excessive tissue growth) can cause increased secretion of estrogen-like substances from the adrenal glands. This can result in symptoms of hyperestrogenism in male dogs, including feminization and other related clinical signs.

Diagnosing estrogen disorders in male dogs involves a combination of clinical assessment, blood tests, and diagnostic imaging. All these tools can aid the veterinarian in diagnosing the cause of the disorders. Treatment will depend on why the dogs have developed estrogen overproduction and whether it is limited to a testicular tumor or an underlying endocrine disorder. Prevention is key when it comes to estrogen related disorders in the male dogs and early castration is proven to almost completely mitigate the develop of estrogen overproduction and improve the dogs overall quality of life.

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Thesis progress report for veterinary students

Name of student: David Hofmeister

Neptun code of the student: C6H8O5

Name and title of the supervisor: Dr. Szilvia Farkas

Department: Department of Reproduction and Farm animal Clinic

Thesis title: Oestrogen-related disorders of dogs

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2022	11	09	Collection of data procedure	
2.	2023	03	23	Analysis of collected data	
3.	2023	04	17	Literature review	
4.	2023	05	30	Case study discussion	
5.	2023	06	23	Analysis of collected data	

Grade achieved at the end of the first semester: .....

Consultation – 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	09	25	Formal requirements	
2.	2023	10	04	Structure	
3.	2023	10	18	discussion of the topic	
4.	2023	10	25	Summary and conclusion	

5.	11	02	2023	Plagiarism	

Grade achieved at the end of the second semester: ..4..

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

.....
signature of the supervisor

Signature of the student: .....

Signature of the secretary of the department: .....

Date of handing the thesis in..17.11.23.....

I hereby confirm that I am familiar with the content of the thesis entitled

Literature review of estrogen-related disorders of the male dog

..... written by David Hofmeister

(student name) which I deem suitable for submission and defence.

Date: Budapest, 15. day Nov. month 2023. year

Dr. Szilvia Farkas

..... Supervisor name and signature

Department of Obstetrics and Food Animal Medicine Clinic

..... Department