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Epidemiology of the 3 most common canine and feline endocrinopathies in different countries: *a literature review*

A kutya és a macska 3 leggyakoribb hormonális betegségének epidemiológiája a különböző országokban: *irodalmi áttekintés*

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Abstract:

In dogs, hypercortisolism, diabetes mellitus and hypothyroidism are considered the 3 most common endocrine disorder. In cats, the most prevalent endocrinopathies are diabetes mellitus, hyperthyroidism and to a lesser extent hypersomatotropism. This thesis evaluated the prevalence of these diseases over time and among countries, with the hypothesis that the prevalence of canine hypothyroidism may decrease over time as the diagnostic tools improved and that the prevalence of canine hypercortisolism and feline hyperthyroidism may increase as the life expectancy of pets increased. And in fact we found, that the prevalence of canine and feline diabetes mellitus, canine hypercortisolism, feline acromegaly and feline hyperthyroidism increased over time. Risk factors of each disease were evaluated, and breeds predisposed to each of these endocrine disorders were described. However, only protected breeds were reported for feline hyperthyroidism, and no breed predisposition has been documented for feline acromegaly. The genetic background of these disorders have recently been investigated as well, and demonstrated not only interbreed but intrabreed susceptibility of some of these endocrinopathies. Various predisposing environmental factors were described for each disease but were of particular importance regarding feline hyperthyroidism.

Összefoglalás:

Kutyákban a hypercortisolismus, a cukorbetegség és a hypothyreosis a 3 leggyakoribb endokrin rendellenesség. Macskákban a leggyakoribb endocrinopathiák a diabetes mellitus, a hyperthyreosis és kisebb mértékben a hypersomatotropismus. Ebben a dolgozatban vizsgáltam e betegségeknek az időbeli és földrajzi előfordulását, azzal a hipotézissel, hogy a kutyáknál a pajzsmirigy elégtelenség előfordulása idővel csökkenhet, ahogy a diagnosztikai eszközök fejlődtek, valamint, hogy a kutyáknál a hypercortisolismus és a macskáknál a hyperthyreosis előfordulása fokozódhat, ahogy a kedvencek várható élettartam növekedett. És valóban, azt találtam, hogy a kutya- és macska diabetes mellitus, a kutya hypercortisolismus, a macska hypersomatotropismus és a macska hyperthyreosis prevalenciája idővel nőtt. Összegyűjtöttem az egyes betegségek kockázati tényezőit, és leírtam az egyes endokrin rendellenességekre hajlamos fajtákat. A macskák hyperthyreosisával kapcsolatban azonban csak védett fajtákról számoltak be, a macskák hypersomatotropismusára vonatkozóan pedig nem dokumentálták a betegségre hajlamos fajtákat. A vizsgált 6 rendellenesség genetikai hátterét csak a közelmúltban kezdték kutatni, és nemcsak fajták közötti, hanem fajtán belüli variabilitást is kimutatták néhány hormonális bántalomra való fogékonysága tekintetében. Különböző hajlamosító környezeti tényezőket leírtak minden egyes betegség esetében, ezek a macskák pajzsmirigy túlműködését illetően különös jelentőséggel bírnak.

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1 INTRODUCTION

Technological advances in veterinary medicine and significant changes in the relationship between owners and their pets over the past 20 years have significantly increased the life expectancy of dogs and cats. This resulted in increased incidence of old age related diseases, such as oncological disorders and some endocrinopathies [1]. In addition, there is a lack of professionals with expertise in the area of endocrinopathies, which accounts for approximately 10% of the total number of veterinary visits for dogs and cats [2]. Consequently, a good knowledge of the characteristics of affected patients as well as the frequency of these diseases helps to recognize endocrine syndromes in the general population. In addition, the description of the most common endocrinopathies within each species allows for better preparation of health professionals, especially in the context of teaching.

Studies describing the prevalence of these diseases often focus on one or a few clinics, sometimes on a region, and rarely across a country. It would therefore be interesting to compare the prevalence of these endocrinopathies across the world. Moreover, breed predispositions may vary among geographical regions, as the demographics of breeds change from country to country. It is also important to note that between different regions, genetic traits may vary within the same breed, and thus could also have an influence in the breed predispositions of these endocrine disorders among different countries.

The most common endocrinopathies diagnosed in dogs are hypercortisolism, diabetes mellitus and hypothyroidism. Among cats, diabetes mellitus, hyperthyroidism and to a lesser extent hypersomatotropism, are the most common endocrine disorders. Most of the overproduction endocrinopathies are the result of neoplasia, most commonly adenomas. This type of disease is usually characterized by a chronic slowly progressive disease in older patient. The other type of endocrinopathy characterized by hormone deficiency is more commonly associated with immune associated process, in younger patients. In this type of endocrine disorder, there is stronger genetic link with family, breed and species predisposition [3].

Over the last decades, technological advances in both human and veterinary medicine improved considerably allowing better diagnostic performances, especially in the diagnosis of endocrine disorders. This is important, as clinical signs may be numerous, diverse, non-specific, and variable between individuals. Great improvements have been made in the complex diagnosis protocol of hypothyroidism over the time [4]. Thus, the prevalence of

canine hypothyroidism may decrease over time as the diagnosis is getting more exact nowadays. Moreover, as the life expectancy of dogs and cats increased, it may be possible to observe an increase in the prevalence of the overproduction endocrinopathies as they are usually related to neoplastic disorders. Thus, the prevalence of canine hypercortisolism and of feline hyperthyroidism may increase over time.

In this work I will focus on the epidemiology and causes of the most common canine and feline endocrinopathies as there are enough data about these to detect any changes of occurrence over time or possible geographical differences. The first part of this literature review discusses the most common canine endocrinopathies, while the second part deals with the most common endocrinopathies reported in cats.

2 MOST COMMON CANINE ENDOCRINOPATHIES

2.1 CANINE HYPERCORTISOLISM – CUSHING'S SYNDROME

2.1.1 CAUSES

Spontaneous hypercortisolism (HC), also known as Cushing's syndrome, results from a chronic overproduction of cortisol [5] and generally results from either a functional pituitary tumor (= Pituitary Dependent Hypercortisolism - PDH) or adrenal tumor (= Adrenal Dependent Hypercortisolism – ADH), although other causes are also recognized [6, 7].

About 80-85% of dogs with naturally occurring HC have **pituitary dependent hypercortisolism** (**PDH**). Pituitary tumors may arise from the pars distalis (about 70%) or from the pars intermedia (about 30%) [8, 9]. While ACTH secretion is episodic in normal dogs, the amplitude and frequency of secretory ACTH bursts are increased in dogs with PDH. Chronic ACTH oversecretion causes excess cortisol production, and thus adrenocortical hyperplasia. Clinical signs of HC are due to the increased exposure to cortisol compared to healthy animals. Feedback inhibition of ACTH secretion from a pituitary adenoma by glucocorticoids is relatively ineffective, as a functioning pituitary adenoma (rarely a carcinoma) autonomously and excessively secretes ACTH.

The second most common cause of canine HC is a **functional adrenocortical tumor** (**FAT**; adenoma or carcinoma) that autonomously produces excessive cortisol, independent of pituitary control. CRH and ACTH concentrations are suppressed by glucocorticoids secreted

by the tumor, causing atrophy of the opposite uninvolved adrenal gland and the non-neoplastic cells of the adrenal gland affected by the tumor. Although bilateral adrenocortical tumors have been described, FATs are usually unilateral.

Besides PDH and ADH, the cause of Cushing's syndrome can also be iatrogenic, as a result of excessive or prolonged glucocorticoid administration that leads to suppressed ACTH levels and adrenal atrophy. Other less common causes include the secretion of ACTH from an ectopic site (tumor), food-dependent cortisol secretion and pituitary hyperplasia caused by excess CRH secretion due to a hypothalamic disorder [6, 7].

2.1.2 EPIDEMIOLOGY AND RISK FACTORS

Prevalence

HC is relatively common in older dogs. Studies from the **USA** estimate the prevalence of PDH to be around 0.2% and the incidence of new HC cases as 1 to 2 cases/1000 dogs/year [10, 11]. In the **UK**, the estimated prevalence of canine HC is 0.28% [12]. Nevertheless, it was diagnosed in more than 1% of dogs in a study of a 15-year period at a **Californian** veterinary teaching hospital, exceeding previous estimates mentioned above [13]. This apparent rise in the prevalence can be due to an increase in the life expectancy of dogs, increased awareness of the disease and the fact that the study was conducted at a referral center, which receives more cases of suspected HC. Thus, it may reflect the difference in prevalence between the general dog population and the "filtered" population presented to referral hospitals. Other studies corroborate this last hypothesis rather than an increased life expectancy in dogs, as suggested in the introduction. In **Italy**, Carotenuto et al. reported in 2019 a prevalence of 0.2% of HC in 4 private clinics while in a University referral center the prevalence was 1.46% [14]. In **North American** veterinary teaching hospitals, the study of Hoffman et al. in 2018 reports a prevalence 10 times higher than other studies, with 2.1% of deceased dogs over 1 year of age having a diagnosis of HC [15]. Regional differences between countries could also be a contributing factor to explain the differences in the prevalence of HC among studies.

Age, gender, neutering status

Spontaneous HC is mostly seen in middle-aged to older dogs. Almost all dogs with HC are older than 6 years at diagnosis [5, 16]. O'Neill et al. (2016) identified increasing risk of HC as animals get older, which has also been reported in other studies [11, 12, 17]. The median age at diagnosis of HC in this study was 10.9 years. Multicenter studies performed in the UK

described 37 dogs with a diagnosis of ADH having a mean age of 11.5 years (sd 1.87 years) and 148 dogs with a diagnosis of PDH having a mean age of 9.6 years (sd 2.3 years) [18, 19]. These ages are similar to the peak cancer incidence in a population of insured UK dogs [20].

There is controversy regarding a possible gender predisposition for HC. Most case series of dogs with PDH, ADH, or with HC independent of cause, report a higher proportion of females (58-75%) [14, 16, 18, 20-24]. Nevertheless, the lack of a control group in all these studies makes it hard to establish a conclusive relationship between gender and HC.

Four studies compared the gender distribution of dogs with HC to a control population, and while two of these studies [12, 26] did not find a difference, the other two identified a female predisposition for HC [14, 15]. These two latter studies also found an association between neutering and increased risk of HC in both males and females.

O'Neill et al. (2016) reported that neutering was associated with higher odds of HC in their univariable analysis, however this association was not described in their multivariable analysis, after accounting for age and other risk factors[12]. Similarly, a recent study describing an American population of dogs diagnosed with HC also failed to identify a difference of HC risk between neutered and intact dogs [10]. In relation to the use of a standardized ACTH stimulation test using a "genderless" reference range for the diagnosis of HC, it is interesting to note that healthy neutered male dogs had higher serum post-ACTH cortisol concentrations than intact males [27]. It has been suggested that entire dogs may require a different reference interval for ACTH stimulation tests and that this group may be currently under-diagnosed if the same reference interval is used as in neutered males [27]. Thus, whether there is a gender predisposition is unclear but nevertheless HC is a disease that can affect both males and females. There is no significant difference in gender distribution between PDH and ADH [23].

Breed predispositions

HC occurs equally in purebreds and mixed-breeds [13]. Smaller dogs, such as **Poodles**, **Dachshunds** and **Terrier breeds** appears to be at higher risk [11, 27-29]. Approximately 75% of dogs affected by PDH weigh less than 20 kg, and almost 50% of dogs affected by FATs weigh more than 20 kg [23]. Familial occurrence of HC has been also described in **Wire-Haired Dachshunds** [31].

The **Standard Poodle**, the **Dachshund**, the **Yorkshire Terrier**, the **Jack Russel Terrier**, the **Labrador Retriever** and the **Bichon Frisé** are the most frequently reported breeds with HC among the 15 case number based studies presented in **Table 1.**

Table 1: Breed predispositions to hypercortisolism in the veterinary literature

Study	Pöppl et al - 2016 [30]	Burkhardt et al - 2013 [28]	Carotenuto et al - 2015 [14]	Fracassi et al - 2015 [29]	Jensen et al - 1997 [32]	van Rijn et al - 2016 [24]	Meij et al - 1998 [33]	van Rijn et al - 2009 [34]	Hanson et al - 2007 [22]	Neiger et al - 2002 [35]	Helm et al - 2011 [19]	Barker et al - 2005 [18]	Kenefick & Neiger - 2008 [36]	O'Neill et al - 2016 [12]	Peterson et al - 1982 [9]	Wood et al - 2007* [25]	Hoffman et al - 2018** [15]	Occurrence in case number based studies	Odds ratio from O'Neill et al - 2016 [12]	Nb studies reporting the breed
Country of the study	**B**	**Sw**	**Italy**		**D**	**The Netherlands**				**UK**					**USA**		**USA+C**		**UK**	
Parameter	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB		RF		OR	
Number of cases	522	40	104	85	18	306	52	17	181	78	37	148	20	304	25			1912		17
Standard Poodle	181				2	4						3			11		>0.3%	10,38%		6
Dachshund	62	4		10	4	23	6		16	6		4	1	10	1	X	>0.3%	7,59%	3.4	14
Yorkshire Terrier		3	7	6		9	4	3	8	9	4	20	4	22	1		>0.2%	5,16%	1.8	14
Jack Russel Terrier		2	2			10				6	2	7	2	29				3,10%	1.5	8
Labrador Retriever	7		5		1	14					8	9		11	1	X	>0.1%	2,89%	0.3	10
Bichon Frisé	17	1										5	1	24				2,48%	6.5	5
Maltese	15		4			16	2	1	8									2,37%		6
Miniature Dachshund	40		6															2,37%		2
Boxer	6		4	9		9					4	9					>0.2%	2,12%		7
Miniature Poodle			6			13	7	1	13								>0.4%	2,07%		6
Beagle	14		2			14	2	1								X	>0.1%	1,70%		7
Shih-Tzu	9	2	2			4								8		X	>0.3%	1,29%	1.8	7
Staffordshire Bull Terrier												7		17				1,24%	0.9	2
Cocker Spaniel	6	1	3			6								7		X	>0.1%	1,19%	0.7	7
CKCS					2	4		1				6		5				0,93%	0.2	5
Doberman Pinscher	17	1															<0.1%	0,93%		3
West highland White Terrier	2	2												13				0,88%	1.1	3
Standard Schnauzer	10		2				2											0,72%		3
German Shepherd	2	1	2			4					1			3			>0.1%	0,67%	0.4	7
English Springer Spaniel								1			2	5	1	2	1		>0.2%	0,62%	0.2	7
Golden Retriever	1					8	2										>0.1%	0,57%		4

B: Brazil; Sw: Switzerland; D: Denmark ; C: Canada ; NB: number of cases ; RF: Relative frequency ; OR: Odds ratio ; CKCS: Cavalier King Charles Spaniel.
* Description of the most common breeds without reporting exact data; ** only the relative frequency reported

However, these studies did not compare the case numbers to the frequency of the given breed in the general dog population (odds ratio), so it is unclear whether the higher occurrence means true breed predisposition or not. One of the only study examining breed predisposition for HC with the odds ratio method in a multivariable logistic regression model for risk factors found **Bichon Frisé, Dachshund**, **Yorkshire Terrier**, **Shih-Tzu** and **Jack Russel Terrier** as most affected breeds [12]. Regarding the **Labrador Retriever**, it was reported in more than half of the studies, but is described as a protected breed in the odds ratio based study of O'Neill et al.

(2016) [12]. This may be explained by the popularity of this breed: although they might show reduced odds of developing HC, they can still contribute substantially to overall HC caseloads.

When looking more precisely at the geographical distribution of breeds predisposed to HC, some breeds appear particularly prevalent in some countries, whereas they are not reported in others. For instance, the **Poodle** is only reported at high risk in North America and Brazil. Inversely, the **Jack Russel Terrier** is not reported in USA and Brazil, while described with high risk in the UK, the Netherlands, and Switzerland. The **Bichon Frisé** is described with higher risk for developing HC almost only in Brazil and the UK. These geographical differences in breed predisposition may be explained by different breed popularities between these countries, but may also demonstrate genetic variability within the breed among countries.

2.1.3 CONCLUSION

HC is mainly caused by PDH and is a common endocrine disorder especially in middle-aged to older dogs. Its prevalence increased over time, although the studies conducted in referral center may have reported an increased prevalence as they receive more suspected cases of HC than primary care clinics. The gender predisposition for HC does not make a consensus among studies, with some studies reporting females to be at higher risk of developing HC while others did not report different prevalence among males and females. Smaller dogs appear to have higher risk of HC. Various breeds have been reported to be at risk for HC, although conclusive interpretations of these data are difficult as most of the studies reporting breeds predisposed to HC did not compare their results to a group control.

2.2 CANINE DIABETES MELLITUS

2.2.1 CAUSES

Diabetes mellitus (DM) is a common endocrine disorder characterized by chronic hyperglycemia resulting from a deficit in insulin production, action, or both. The most common form of DM in dogs is **type 1 diabetes mellitus**: a permanent hypoinsulinemia in which there is no increase in endogenous serum insulin or C-peptide concentrations following administration of an insulin secretagogue (glucose, glucagon, amino acids). With rare exception, all diabetic dogs require a life-long exogenous insulin therapy in order to manage their hyperglycemia and to avoid ketoacidosis [37, 38].

Histological observations from pancreatic tissue of diabetic dogs involve a reduction in the number and size of the pancreatic islets, a decreased number of β-cells within the islets, and β-cell vacuolization, enlargement and degeneration [39]. The underlying cause of the destruction/ dysfunction of pancreatic β-cell is not established yet. In humans and dogs, DM is undoubtedly a multifactorial disease involving both genetic and environmental factors [31, 35-39].

The concept of genetic predisposition has been based on familial associations, pedigree analyses of Keeshond and other breeds, and genomic studies [40-42]. Canine DM has been associated with major histocompatibility complex (MHC) class II genes (dog leukocyte antigen; DLA). DLA group of genes are mainly involved in the regulation of the immune system, and are associated with many auto-immune diseases and endocrine dysfunctions in dogs, with similar haplotypes and genotypes identified for the most susceptible breeds [49, 50]. These include DM [47, 50], immune mediated hemolytic anemia [51], hypothyroid disease [52, 53], anal furunculosis [54] and polyarthritis [55]. The findings of Gershony et al. in 2019 build upon previously published data to suggest that the two-locus (DQ) model serve as a good indicator for susceptibility to multiple organ-specific autoimmune diseases in the canine population [56]. However, it is also clear that additional loci are necessary for actual disease expression. Immune-mediated insulitis has been described and antibodies directed against islet cells, insulin, proinsulin, intracellular glutamic acid decarboxylase 65 (GAD65), and insulinoma antigen 2 (IA-2) have been identified in diabetic dogs [52-56]. The reviews of Denyer in 2021 allow a deep understanding about the current knowledge on the genetics of human and canine DM and about the directions of the research in the future [62, 63].

Presumably, autoimmune mechanisms, in conjunction with genetic and environmental factors, insulin-antagonistic diseases and drugs, and pancreatitis all play a potential role in the initiation and progression of diabetes in dogs. The end result is a loss of β-cell function, hypoinsulinemia, impaired transport of circulating glucose into most cells, accelerated hepatic gluconeogenesis and glycosuria.

Obesity-induced insulin resistance has been documented in dogs but progression to type 2 diabetes does not occur [64]. Studies suggest that at least some of the etiopathogenetic mechanisms responsible for the development of obesity-associated type 2 diabetes in humans and cats do not occur in dogs. Diabetes may occur secondary to disorders of the exocrine pancreas and any process that diffusely injures the pancreas can cause diabetes, especially **pancreatitis**. The incidence of histologically identifiable, often severe pancreatitis in diabetic dogs is 30-40% and is believed to be a contributing factor in the development of diabetes and

diabetic ketoacidosis in affected dogs [60-62]. Subclinical diabetes can be caused by the administration of **diabetogenic drugs** (glucocorticoids and progestins in particular), as well as concurrent hormonal diseases, such as **HC**, or diestrus-induced growth hormone excess, causing a **diestrus-induced diabetes**. Older females are frequently diagnosed with DM while in diestrus (whether pregnant or not), when serum progesterone and growth hormone are increased, which antagonize the effects of insulin [63-65].

2.2.2 EPIDEMIOLOGY AND RISK FACTORS

Prevalence

The prevalence of canine DM has been estimated from about 1.33% in dogs in referral institutions (**USA**: 0.64% ; **Italy**: 1.33% ; **India**: 1%) to about 0.3% in first opinion practice (**UK**: 0.3-0.34%; **Australia**: 0.36%). [41, 66-70]. The reported incidence of DM in a population of 182 087 insured dogs in **Sweden** was about 13 cases per 10 000 (0.13%) DYAR (dog-years at risk) [45]. Recently, and for the first time in Africa, the prevalence of DM in canine population was studied, and estimated at 0.22% in **Nigeria** [76].

The prevalence of canine DM presented to veterinary teaching hospitals in **North America** increased from 19 cases per 10,000 admissions per year in 1970 to 58 cases per 10,000 in 1999 [46]. The same tendency has been reported later in other clinics, with 13 cases in 2006 to 23.6 cases per 10 000 in 2015 [77]. It is interesting to highlight the fact that simultaneously with the increase in the prevalence of DM, a decrease in the case-fatality rate from 37% to 5% has been reported [46]. It has been suggested that owners and veterinarians are now more willing to undertake long-term management of diabetic dogs and that advances have been made in the nutritional management of diabetic dogs.

Age, gender and neutering status

DM is diagnosed in middle-aged and older dogs, from 5 to 12 years of age, with a peak prevalence at 7 to 10 years of age [45, 46, 71]. Rarely DM in juvenile dogs has been reported [71, 78].

Regarding any gender predisposition, most, but not all, studies suggest that females are at greater risk [45, 46, 71, 79]. The proportion of females has decreased from more than 70% to around 55% in the UK, most probably because of more frequent early neutering and the consequent decrease in diestrus-associated diabetes [71, 79]. Pathogenesis of DM in entire female is often associated with progesterone dominated phase of diestrus and release of growth hormone (GH) from mammary glands into the circulation resulting in insulin resistance [70, 80]. The study of Fall et al. (2007) showed indeed a higher incidence of DM in females (72%),

which can be explained by the fact that spaying of bitches in Sweden is rare and performed most often late in life [81]. Neutering of females may decrease the risk of developing DM as sterilized females will not develop diestrus-associated diabetes. However, the effect of neutering in male seems to predispose to DM. Neutered dogs in several studies are reported at increased risk compared to intact males [46, 74, 82]. One possible explanation is that male-sex hormones may have a protective effect against DM, although other factors associated with neutering, such as obesity, may also have an influence [74]. Variation in neutering practices may thus influence sex predispositions within a population, although associations identified between neutering and diagnosis of DM also vary.

Seasonality

A 3 year survey of practicing veterinarians in the State of Wisconsin revealed a strong seasonal variation (peak incidence in January and February) for spontaneous canine DM dogs [83]. Seasonal pattern of new DM cases in dogs were found in other studies as well. Davison et al. (2005) reported a peak between October and March, while Fall et al. (2007) reported on spring predisposition (April-June). This is consistent with the findings of Mattin et al. (2014), who described higher proportions of diagnosis in winter and spring. Although several studies report seasonality in the diagnosis of DM, others failed to describe it [46, 79, 82]. Although the impact of seasons on the onset of diabetes in dogs remains unclear so far, it is suggested that there may be underlying similarities with people in environmental factors. In humans, several factors such as viral infections occurring mostly in winter months [84], as well as dietary changes, obesity, inactivity and climatic change are involved in the development of DM [85]. Some of these factors may act as a triggering event in the same manner in dogs resulting in the development of canine DM [71].

Breed predispositions

Epidemiological studies have identified breed differences in the susceptibility to DM [37, 45, 46, 72, 79, 86], suggesting a genetic component to this complex disease [37]. As presented in **Table 2**, ***Samoyed***, many ***terrier breeds*** and ***Schnauzers*** are frequently reported as predisposed breeds, whereas ***German shepherds***, ***Boxers*** and ***Golden Retrievers*** are described as having a decreased risk of DM.

Table 2: Breed predispositions to canine diabetes mellitus in the veterinary literature

Study	Kennedy et al - 2006 [47]	Kennedy et al - 2006 [47]	Catchpole et al - 2013 [48]	Mattin et al - 2014 [74]	Fracassi et al - 2004 [72]	Hess et al - 2000 [86]	Guptill et al - 2003 [46]	Yoon et al - 2020 [75]	Fall et al - 2007 [45]
Country of the study	**UK**				**Italy**	**USA**		**Australia**	**Sweden**
Parameter	Risk group	**OR**	**OR**	**OR (multi)**	OR (uni)	**OR (uni)**	**OR (multi)**	**OR (multi)**	IR
Australian Terrier							31.1	7.93	183
Samoyed	High	17.3	35.84			11.83	3.36		104
Cairn Terrier	High	6.77	9.76				2.07		21
Tibetan Terrier	High	6.93	10.39						
Swedish Lapphund									72
Swedish Elkhound									45
Drever									36
Finnish Hound									36
Hamilton Hound									29
Tenterfield Terrier								3.67	
Scottish Terrier			3.35						
Standard Schnauzer							4.78	3.18	
Miniature Schnauzer	Moderate	3.18	3.62			9.87	3.13	3.47	20
Border Terrier	Moderate	2.4	1.8	3.49					8
Yorkshire Terrier	Moderate	3.48	1.55	4.56	2.62	1.88			7
West Highland White Terrier	Neutral	1.7	3.04	1.99				4.85	33
Fox Terrier							3.02	1.64	
Keeshond							2.45		
Pug						3.87		1.81	
Bichon frise	Moderate	3.6	1.51	2.27		2.12	2.4	3.41	17
Border Collie	Moderate	2.89	2.02	2.22				1.03	
Dachshund (all types)	Moderate	2.83	4.07			1.06		1.27	9
Finnish Spitz							2.32		
Poodle (all types)			2.38		2.8	4.01	1.79	3.41	24
Husky			3.46				1.53	6.24	
Lhasa apso						2.26		0.9	
Chihuahua						1.49		0.63	
Beagle			0.99				0.67	0.5	24
English Setter					2.6		0.61		
Labrador	Neutral	0.97	1.67	0.54		1.13	0.58	1.08	13
Dalmatian							0.53	1.89	10
Dobermann	Neutral	1.22	4.05		0.13		0.51		
Irish Setter					3.91		0.48		13
Rottweiler	Neutral	1.74	0.69			0.59		1.33	23
CKCS	Neutral	1.45	1.41	2.54				1.84	15
Cocker Spaniel	Neutral	0.75	1.25	1.48		0.42	0.25	0.73	8
Jack Russell Terrier	Neutral	1.48	0.61	1.17				0.89	6
Springer Spaniel			0.58			1.33		5.37	13
Shih Tzu							0.38	1.59	6
Elkhound							0.33		17
Bull Terrier				0.31		0		0.49	
Golden Retriever	Protected	0.19	0.73	0.12		0	0.31	0.09	0
Shetland Sheepdog							0.23		10
German Shepherd	Protected	0.15	0.23	0.06	0.11	0	0.16	0.11	4
Airedale Terrier							0.15		
Boxer	Protected	0.07	0.07		0		0.07	0	0

OR (uni): Odds ratio (univariable) ; OR (multi): Odds ratio (multivariable) ; CKCS: Cavalier King Charles Spaniel ; IR: Incidence Rate cases per 10,000 DYAR

Among those studies, the breed susceptibility to DM can vary greatly. For example, breeds with the highest risk for DM in the **UK** include ***Samoyed***, ***terrier dogs*** (***Cairn***, ***Tibetan***, ***Yorkshire***, ***Border***), ***Schnauzer*** (miniature and standard), ***Bichon Frise***, and ***Border Collie***. In **Italy**, the most susceptible breeds for DM include ***Irish Setter***, ***Poodle***, ***Yorkshire Terrier*** and ***English Setter***. In **Sweden**, high risk breeds included Spitz type breeds (***Samoyed***, ***Swedish Elkhound***, and ***Swedish Lapphund***) and Scandinavian hound dogs (***Finnish Hound***, ***Hamilton Hound***, and ***Drever***). In **USA**, high risk breeds included ***Australian Terrier***, ***Schnauzer***, ***Samoyed***, ***Fox Terrier***, ***Poodles*** and ***Bichon Frisé***. The study conducted in **Nigeria** did not report on breed predisposition, as there were only 6 dogs with DM in the study [76]. A very recent epidemiological study in **Australia** reported ***Australian terrier***, ***Husky***, ***English springer spaniel***, ***West Highland white terrier***, ***Schnauzer***, ***Poodle*** and ***Bichon Frisé*** being the highest risk breeds for DM in dogs.

Interestingly, some breeds are described to be at risk only in some countries (see **Table 2**). For example, ***Border Collie*** and ***Dachshunds*** are only reported at risk in **England**, while are considered neutral in other countries. ***Samoyed*** is not at risk in **Australia** and **Italy** whereas it is highly prevalent in other countries. ***Husky*** is at increased risk in **Australia** and the **UK** while not described in other studies. ***Dobermann*** is reported at risk in one study in the **UK** but neutral in another one, and even protected in **Italy**. ***English Springer Spaniel*** is at high risk in **Australia** but described as protected in one study in the **UK**.

These data suggest that there is an intrabreed variability according to the regions of the world, which could be explained by different factors. Firstly, some breeds are overrepresented in some countries while absent or almost absent in others. Secondly, not all studies reporting the prevalence of susceptible breeds compared their results with control groups of the whole population. Finally, these intra- and interbreed variabilities among countries supports the hypothesis of an underlying genetic component in the development of DM.

Recently, several studies investigated the genetic basis for canine DM conducting genome sequencing in high risk and protected breeds and described specific variants in regions of the genome contributing to the susceptibility of DM [42, 80-82]. However, these studies are usually performed in a limited region or a country, and may not reflect the genetic specificities of a breed but only of a sub-population. Thus, worldwide sampling of pure-breed dogs sharing the same disease may increase power of finding a locus related to a susceptibility to a disease. However, it may also increase the likelihood of false positive results as intrabreed variability can exist in some breeds. Over representation of a rare allele can lead to the conclusion that a linked marker

has been found when, in fact, the frequency of the allele reflects the relatedness of cases in the population. It is therefore important to determine the extent to which dog breeds may be sub-divided into smaller genetically differentiated entities, especially for cohorts sampled from different countries [90]. Knowing the extent of intrabreed sub-structure will increase the likelihood that results from whole genome association studies carried out on collections of dogs from single breeds are accurate [90]. Regarding this matter, the study of Kennedy et al. (2002) reported that the DLA class II genes, which have been described as related to DM in dogs, have a high interbreed but a low intrabreed variation of MHC alleles and haplotypes [91].

2.2.3 CONCLUSION

Canine diabetes mellitus is a common endocrine disorder in dogs, with an increased prevalence over time, and a decreasing rate of case-fatality. This endocrinopathy affects middle-aged to older dogs, and bitches are generally described to be at greater risk compared to males due to the periodic influence of diestrus-associated insulin resistance. Several studies reported breeds at different level of risks for developing DM. Diverse breeds were described at high risk, others at moderate risk or neutral, and finally some were reported as protected breeds for DM. Interestingly, there is not only evidence for interbreed differences but also intrabreed variabilities for the susceptibility of DM worldwide. Moreover, evidence is mounting for a genetic basis of canine DM, and the association with the major histocompatibility complex alleles on the dog leukocyte antigen strongly suggests an important role of the immune response in the development of canine DM. Although there is no sure evidence of obesity being a direct risk factor for DM in dogs, obesity is a risk factor for pancreatitis, which may cause DM [43].

2.3 CANINE HYPOTHYROIDISM

2.3.1 CAUSES

Canine hypothyroidism (HOT) can develop due to thyroid gland destruction, decreased stimulation by TSH from the pituitary gland, or failure in any of the steps of thyroid hormone synthesis. HOT is the most common thyroid disorder in dogs and may be acquired or congenital. It can also be primary when the thyroid gland is directly affected, or central – due to TSH or TRH deficiency (secondary or tertiary HOT, respectively).

Acquired primary HOT is the most common cause of naturally occurring failure of the thyroid gland in dogs. Two histologic forms are described: lymphocytic thyroiditis and idiopathic atrophy, both being equally common among dogs.

Lymphocytic thyroiditis is a destructive autoimmune process characterized by multifocal/diffuse infiltration of the thyroid gland by lymphocytes, macrophages and plasma cells and progressive replacement by fibrous tissue [92, 93]. Destruction of the thyroid gland is progressive, and clinical signs do not develop until at least 80% of the gland has been destroyed. Graham et al. (2007) proposed four stages in the progression of lymphocytic thyroiditis in dogs [94]. The first stage (subclinical thyroiditis) is characterized by focal and often peripheral lymphocytic infiltrates in the glands, with positive thyroglobulin and thyroid hormone autoantibody tests, with a normal histologic appearance otherwise. The stage 2 (antibody positive subclinical HOT) appears when more than 60 to 70% of the thyroid mass underwent pathologic change, with a compensatory elevation of serum TSH concentration, stimulating the thyroid gland to maintain normal T4 concentration. In stage 3 (autobody positive overt HOT), nearly all functional thyroid tissue has been destroyed by inflammation, T4 production cannot be maintained, and the classic laboratory pattern with decreased total T4, increased TSH and positive antibody tests is found. The noninflammatory atrophic HOT is the 4th stage characterized by replacement of thyroid tissue by fibrous and adipose tissue and disappearance of inflammatory cells and circulating antibodies.

Idiopathic atrophy of the thyroid gland is a degenerative process with minimal inflammatory changes and gradual replacement of the thyroid tissue by adipose and connective tissue. It may be either a primary degenerative disorder [92] or the end stage of lymphocytic thyroiditis. To support this hypothesis, the study of Graham et al. (2001) reported that the mean age of dogs with suspected idiopathic atrophy was higher compared to dogs diagnosed with lymphocytic thyroiditis [95]. Unlike for lymphocytic thyroiditis, there are no blood tests establishing the diagnosis of idiopathic atrophy. Thus, the diagnosis is made by exclusion: if the antibody tests for lymphocytic thyroiditis are negative, a diagnosis of idiopathic atrophy can be made [1].

Among the rare causes of acquired primary HOT ingestion of goitrogens, the administration of anti-thyroid drugs (e.g., propylthiouracil and methimazole), and the long-term high dose application of potentiated sulfonamides should be mentioned. A palpable goiter may develop in dogs treated chronically with potentiated sulfonamides [96, 97]. Iodine deficiency can also be a cause of HOT in dogs but remains rare because commercial pet foods contain the required amount of iodine. Nevertheless raw food diets are more and more given to dogs, which can be

deficient in iodine [98]. A study reported clinical HOT due to iodine deficiency in working dogs fed all meat diet [99]. Interestingly, the excessive intake of iodine inhibits its uptake and organification by thyroid follicular cells, resulting in a small compensatory increase in circulating TSH concentrations [100]. Thus, diets too rich in iodine caused impaired thyroid function and HOT in puppies [101].

Central HOT is rare, accounting for <5% of hypothyroid dogs, caused mostly by pituitary neoplasia or surgical hypophysectomy. HOT due to central causes is less severe than primary HOT [103]. Secondary HOT is a potential uncommon reversible condition due to glucocorticoids excess [36, 102].

Congenital primary HOT may result from various forms of thyroid dysgenesis (e.g., athyreosis, thyroid hypoplasia) or from dyshormonogenesis (usually an inherited defect of thyroid hormone synthesis) [104]. This form of HOT is rare, however, some cases could remain undiagnosed as they die at birth or shortly thereafter [1].

Congenital secondary HOT (associated with clinical signs of disproportionate dwarfism, lethargy, gait abnormalities, and constipation) has been reported in a family of Giant Schnauzers [105], and a Boxer dog [101-104].

Congenital HOT with goiter as a result of dyshormonogenesis and thyroid peroxidase (TPO) deficiency was reported sporadically as a fully penetrant autosomal recessive disorder in Toy Fox and Rat Terriers for whom genetic tests are available [104, 110, 111]. In the affected dogs of both breeds the same mutation was found in the gene encoding TPO. It is suggested that this mutation was crossed into Rat Terriers from Toy Fox Terriers. In the study of Pettigrew et al. (2007), Rat Terrier puppies with congenital goiter suffered from hypomyelination of the central nervous system [111]. The hypomyelination was regionally distributed and most severe in the corpus callosum. Myelin reduction was paralleled by axon reduction, suggesting that hypomyelination was due to reduced axonal formation. Other mutation with similar phenotype have been reported in Tenterfield Terriers, Spanish Water Dogs and Papillons [110, 112, 113].

Another type of congenital secondary HOT has been reported in German Shepherds, with pituitary dwarfism associated with a cystic Rathke's pouch appearing at an early age in life. In these puppies, TSH deficiency is concurrent with deficiencies of GH and prolactin, while secretion of LH and FSH is less severely impaired [114, 115]. In these dogs, manifestations of HOT are overshadowed by those of GH deficiency, in part because 10-15% of thyroid gland function is independent of TSH.

2.3.2 EPIDEMIOLOGY AND RISK FACTORS

Prevalence and challenges of diagnosis

HOT is the most common thyroid disease and one of the most common endocrine disorders in dogs. Its prevalence has been estimated between 0.2 and 0.87% [111-114]. In **North America**, the prevalence in 1981 was estimated at 0.29% [117], another study in **USA** reported a prevalence of hypothyroid dogs of 0.2% among dog population [118]. In **Sweden**, the prevalence appears to be very low with 0.07% of dogs affected with HOT, although it was described as the most common endocrine disorder seen in Swedish dogs [120]. In Sweden, the specific prevalence of HOT in dogs was investigated only in one breed, reporting that 2.7% of Gordon Setter had HOT [119]. Recent epidemiological studies in **India** reported a prevalence of 0.174% in Punjab [121], and 0.4% in Haryana [122]. Another study investigated the prevalence of HOT in 3 different regions of India and reported that 1.28% of dogs were affected by HOT in Chhattisgarh state, 1.73% in Raipur, 1.25% in Durg-Bhillai and 0.97% in Rajnandgaon [123]. The difference noted in the prevalence rate in various districts could be due to a variation in sample size of these studies. Moreover, only tT3, tT4 and fT4 were estimated by Radio Immuno Assay (RIA) kits to test the thyroid function in this study, which might have led to overestimation of HOT compared to other epidemiological studies mentioned above.

As a matter of fact, diagnosis of HOT is challenging, and different methods are used to diagnose HOT. Thus the paucity of accurate data due to challenges of diagnosis were identified as the major cause of variable prevalence of this endocrine disorder [94]. In their study, Dixon et al. (1999) [116] stated that the epidemiological, clinical, hematological and biochemical characteristics of HOT have been complicated by a lack of consistency in the diagnostic criteria applied, particularly the use of what are now often considered unreliable diagnostic tests [117, 124]. Nowadays, a great variety of tests are available, but recommendations for their use and interpretation vary. It is now recognized that the diagnosis of HOT is largely based on the analysis of basal thyroid hormone analyses, endogenous canine TSH and the presence of thyroglobulin autoantibodies (TgAA), all of which have significant differences in diagnostic performance [4]. It is also recommended to perform thyroid-imaging techniques (scintigraphy) or TSH stimulation testing if the use of the previously mentioned standard tests have borderline results. The literature review by Mooney (2011) provides a protocol for the diagnosis of HOT using the most frequently recommended tests [4].

While interpretating tests of thyroid gland function, it must be considered that there are many factors influencing baseline thyroid hormone and endogenous TSH concentrations.

Age, breed, body size, athletic training, diurnal or random fluctuations, gender, reproductive status, concurrent illness and drug therapy can all have an influence on the thyroid hormone concentrations, many of them decreasing the baseline concentration, while some can also increase endogenous TSH in euthyroid dogs [1]. The most common factors lowering baseline thyroid hormones concentrations in euthyroid dogs described by Feldman et al. (2015) are concurrent illness, also known as nonthyroidal illness syndrome (NTIS), use of glucocorticoids or other drugs, and random fluctuations in thyroid hormone concentrations [1]. Misdiagnosis of HOT may happen if these factors are not taken in account in the interpretation of test results.

Several studies have demonstrated that concentrations of thyroid hormones in serum differ greatly from one breed to another [120-125]. It has been first reported that total thyroxine (TT4) concentrations were greater in small breeds compared with medium or large breeds [131]. Greyhounds have been described as having significantly lower serum T4 and fT4 concentrations compared to non-Greyhounds [126, 129]. Similarly, other breeds were reported to have T4 concentrations at or below the lower limit of previously established reference range for T4. These breeds are the Scottish Deerhound [132], the Alaskan sled dog [127, 128], the Sloughi [133] and the Basenji [134]. Hegstad-Davies et al. (2015) conducted a study selecting high risk breeds for HOT and reported a significant breed-associated variability in serum concentrations of T4, fT4 and TSH [135]. Thus, the previously established reference intervals (RIs) could not be accurate enough regarding the lower limit of the RI. With this currently used non-breed specific RI, healthy dogs from these breeds could be misdiagnosed as being hypothyroid, and the prevalence of HOT in these breeds could be overestimated. The use of breed-specific RI, warranted for the 7 breeds studied by Hegstad-Davies et al. (2015) should allow more accurate interpretations of thyroid hormones tests in the process of diagnosis of HOT [135].

Regarding the hypothesis that HOT may decrease over time as the diagnosis is getting more exact, the literature cannot confirm it. The data about the prevalence of this disease are too sparse, the size of the population studied varied greatly, the methods used for the assessment of HOT make the comparison difficult to analyze, and even very recent studies did not use the recommended protocol to confirm the diagnosis of HOT [123].

Age, gender and neutering status

HOT is typically a disease of middle-aged to older dogs. The mean age at diagnosis is approximately 7 years and ranges from 0.5 to 15 years [116, 118]. It is uncommon diagnosis in dogs less than 2 years of age [136]. Breeds predisposed to lymphocytic thyroiditis tend to

develop subclinical HOT at an earlier age (2 to 4 years) compared to the age of the development of clinical signs (4 to 6 years) [94], which reinforces the theory that thyroiditis may evolve to complete thyroid failure over time [1]. The study of Graham et al. (2007) described the age distribution of dogs with thyroid disease through analyses of TgAA in the serum of 143,000 dogs as a marker for the prevalence of thyroiditis [94]. The subclinical thyroiditis is seen mostly in 2 years old dogs, the antibody positive subclinical HOT in 4 years old dogs and noninflammatory atrophic HOT in 5 to 8 years old dogs.

While some studies reported a higher prevalence of HOT in females [117, 122, 137, 138], one described males as more predisposed [123]. Others, however, did not find a significant difference between male and female dogs in regard to prevalence of HOT [111, 134-136]. Neutering was described as a significant risk factor in females [117, 118], and males [117], although these findings have not been reported by other studies [116]. This could indicate that sexually intact male and female dogs may be slightly protected from this autoimmune disease.

Breed predispositions:

Reported breed predispositions, together with the familial nature of HOT in purebred dogs allow to confirm a strong hereditary component to this disease [13]. Genetics plays a main role, especially given the increased incidence of HOT in several breeds. Lymphocytic thyroiditis has been described as an inherited disorder in colony-raised ***Beagles*** with a polygenic mode of inheritance [1]. Conaway et al. (2007) reported an autosomal recessive mode of inheritance for lymphocytic thyroiditis in ***Borzoi*** dogs [142]. Familial HOT is recognized in ***Great Dane***, ***Beagle*** and ***Borzoi*** colonies, and in ***Hovawarts*** and ***Giant Schnauzers*** in Sweden [135, 137-139].

Several genetic and environmental risk factors have been described regarding the development of autoimmune thyroid disease in humans but are not reported as clearly in dogs. Immune-mediated diseases are likely to have a genetic component in their etiology and this is supported by increased breed predisposition or resistance. In dogs, specific major histocompatibility (MHC) dog leukocyte antigens (DLA) haplotypes and alleles (certain DLA class II haplotypes) are responsible for an increased susceptibility for HOT in ***Dobermann Pinschers***, ***Rhodesian Ridgebacks***, ***English Setters***, ***Boxers*** and ***Giant Schnauzers*** [140-143]. The study of Kennedy et al. (2006) revealed a raise in DQA1*00101 allele in the ***Doberman Pinscher***, ***Rhodesian Ridgeback*** and ***English Setter***. In the ***Boxer***, the data are suggestive of a different MHC association which confers a specific haplotype to the breed.

The two most commonly described breeds at high risk for HOT are the ***Golden Retriever*** and the ***Doberman Pinscher*** **(Table 3)** [89, 111-113, 141, 143]. Furthermore, Milne and Hayes (1981) also described the ***Irish Setter***, the ***Airedale*** and the ***Shetland Sheepdog*** breeds with high risk of HOT [117]. In a more recent study by Nachreiner et al (2002) ***Pointers, English Setters, Skye Terriers*** and ***Old English Sheepdogs*** were additionally identified as most predisposed [138]. Using age-distribution profiles on a breed-specific basis, there is some evidence that there may be different progression rates among breeds. These breeds include the ***English Setter***, the ***Golden Retriever***, the ***Rhodesian Ridgeback***, the ***Cocker Spaniel*** and the ***Boxer*** [94]. Moreover, an increased incidence of anti-thyroglobulin antibodies have been reported in the ***Great Danes*** [144], the ***English Cocker Spaniels*** [144], the ***English Setter***, the ***English Pointer***, the ***Skye Terrier***, the ***German short hair pointer***, the ***Old English Sheepdog***, the ***Boxer***, the ***Maltese***, the ***Kuvasz*** and the ***Petit basset griffon Vendeen*** [138] although it can develop in dogs of any breed.

The ***Labrador Retriever*** is frequently reported as one of the most prevalent breeds with HOT as well. This breed has been described as sharing the same risk haplotype as the Doberman Pinscher and the Giant Schnauzer but without quoting any reference [148], or referencing unpublished data [146]. Milne and Hayes (1981) reported an odds ratio of 1 for Labradors so neither at high risk nor protected from HOT [117]. The high prevalence of this breed among studies may be because Labrador Retriever is one of the most common breeds around the world.

The **German Shepherd** is reported to be at risk in India [121, 123, 137], but is otherwise not described at predisposed, or is reported as a protected breed [117]. HOT in the **Beagle** also has increased incidence in closed breeding colonies in the UK [140], and in one study in Brazil [30], but is not reported predisposed for HOT elsewhere. These differences may reflect genetic variation of breeds in different regions of the world, and need to be further investigated.

It is important to emphasize that epidemiologic studies of HOT are particularly sparse compared to studies focusing on HC and DM in dogs. Only the study by Milne and Hayes (1981) considered the epidemiologic features of HOT in dogs, and reported breed predispositions in the form of odds ratio analysis **(Table 3)** [117]. Most reports did not compare their results to a group control [30, 94, 121, 123], which make the interpretation of their results and their comparison difficult. Breed popularity and geographic variation in breed distribution may in fact strongly influence the perception of high-risk breeds for HOT. In addition to that, the confirmation of a definitive diagnosis of HOT being challenging, studies reporting breed incidence and genetics of canine HOT should always be evaluated critically.

Table 3: Breed predispositions to hypothyroidism in the veterinary literature

Study	Milne and Hayes - 1981 [117]	Peterson et al - 1998 [149]	Nachreiner et al - 2002 [138]		Graham et al - 2007 [94]		Kennedy et al - 2006 [53]		Kour et al - 2020 [121]	Roopali et al - 2020 [123]	Pöppl et al - 2018 [30]
Country of the study	**USA + C**	**USA**	**UK**						**India**		**Brazil**
Diagnostic method	Cholesterol, T4, T3, histopath	TT4, fT4, TSH, T3	THAA		NA	TgAA+	Full hypothyroid panel test *		T4, TSH	tT3, tT4, fT4	NA
Parameter	**OR**	NB	NB	OR	NB	TgAA+	NB	C	NB	%	%
Number of cases	**3206**	**54**	**287948**		**11606**		**173**	**267**	**35**	**42**	**160**
Doberman Pinscher	3.6	5	11084	1.24	527	26%	32	21			0.6
Irish Setter	3		2534	1.1	42	62%	2	5			
Airedale Terrier	3		1516	0.84							
Shetland Sheepdog	2.3	2	11423	1.69	698	57%	2	2			
Golden Retriever	2.2	8	36016	1.9	1525	69%	2	16		19.05	1.9
Pomeranian	1.9		2025	0.41	42	21%				9.52	
Dachshund	1.6		7438	0.41	81	16%			2		11.3
Cocker Spaniel	1.5	6	18976	1.17	1134	60%	1	2			3.8
Miniature Schnauzer	1.5		1373	0.48							
Pug	1.3		1150	0.58					7	7.14	1.9
Saint Bernard	1.1		549	0.83						2.38	
Labrador Retriever	1	2	26954	0.61	953	39%	4	14	18	50	6.9
Collie	1		3276	0.49	121	21%	1	2			
Poodle	0.9	2	6216	0.46	90	24%					5.6
Chihuahua	0.9		963	0.4							
Boxer	0.8	2	5239	2.37	259	64%	12	22			1.3
Beagle	0.8		3988	1.79	516	53%	1	9			12.5
Mixed Breeds	0.5	6	42647	1.05	2535	51%	6	12	1		24.4
German Shepherd	0.5	2	6594	0.53	151	33%	3	14	2	9.52	0.6
Pointer			118	3.61							
English Setter			1246	3.44	73	84%	17	44			
English Pointer			99	3.31							
Skye Terrier			53	3.04							
German Short Hair Pointer			324	2.72			1	0			
Old English Sheepdog			1031	2.65							
Maltese			962	2.25	91	57%					1.9
Kuvasz			180	2.18							
American Staffordshire Terrier			246	1.84			2	6			0.6
American Pit Bull Terrier			676	1.78	44	57%			1		1.3
Dalmatian		4	2332	1.74	262	58%	1	3			0.6
Rhodesian Ridgeback			1025	1.72	42	64%					
Chesapeake Bay Retriever			1005	1.56	51	71%	26	15			
Husky			1153	1.45	119	62%					
Brittany Spaniel			1257	1.42	69	48%					
Australian Shepherd			1328	1.28	63	51%					
Malamute			1449	1.22	66	45%					
Border Collie			227	1.05	75	59%	1	2			0.6
Akita			2579	0.74	44	50%	1	2			0.6
Samoyed			1921	0.71	53	43%			3		
Schnauzer			1681	0.7	59	49%	1	4			
Rottweiler			4568	0.61	162	37%	3	4		2.38	3.1
Springer Spaniel			3452	0.54	113	34%	3	6			
Chow chow			2797	0.5	81	35%					0.6
Shih Tzu			3322	0.29	45	31%			1		0.6

NA: Not described in the study; THAA: Thyroid hormone autoantibodies (for T3 and T4) ; NB: Number of cases ; OR: Odds ratio ; TgAA+: Proportion of TgAA-positive among the hypothyroid dogs ; C: Control ; %: percentage of the number of hypothyroid dogs of the breed compared to all the hypothyroid dogs of the study

* TGAA%, TT4, TT3, FT4, FT3, thyroid hormones autoantibodies (for T3 and T4) and CTSH

2.3.3 CONCLUSION

HOT is mostly an acquired primary disorder with failure of the thyroid gland, caused by either lymphocytic thyroiditis or idiopathic atrophy. Its prevalence is estimated between 0.2 and 0.8% [111-114], and does not seem to decrease with time, invalidating the hypothesis stated in the introduction. Regarding breed predispositions, most of the studies made a consensus for the most important high-risk breeds, however highlighted various other breeds not reported in other studies. The whole challenge while studying HOT is that reliable interpretation of the findings as well as precise calculation of real breed prevalence are difficult. It is complicated by the different criteria used for the diagnosis of HOT across studies, but also by the various factors that can influence the thyroid function tests, the inherent problems of bias in hospital populations, the different breed popularities across time and countries and the potential variation in the genetic make-up within the same breed in different dog populations.

3 MOST COMMON FELINE ENDOCRINOPATHIES

3.1 FELINE DIABETES MELLITUS

3.1.1 CAUSES

Based on clinical presentation, epidemiology, genetic research and association with islet amyloid deposits, diabetes mellitus in cats has been classified as a **type 2 diabetes mellitus** (T2DM) [150, 151]. This disorder is characterized by insulin resistance with concomitant failure of β-cells to build up a correct compensatory response in order to maintain euglycemia [152]. This T2DM is the most common form of DM seen in cats, and as in humans, it is associated in cats with obesity and physical inactivity as a major risk factor [153, 154] together with older age. Clinical and endocrine characteristics are similar as well, with a potential for insulin independence, variable insulin secretion and remission, and islet vacuolization and amyloid deposition [149-151]. The T2DM appears to account for about 80-90% of diabetic cats examined at primary care veterinary practices in Western countries based on clinical and phenotypic characteristics, as well as remission rates [43, 158].

Type 1 diabetes mellitus (T1DM) is the most common form in dogs, but it is rare in cats, based on histological studies and absence of circulating β-cell autoantibodies [159, 160]. However, histologic findings, clinical presentation and islet cell antibodies consistent with

T1DM were reported in a 5-month-old kitten [161]. The study of Zini et al. (2012) examined islets lesions in a group of 27 diabetic cats compared to a control group (matched in age, sex and body weight), and in 20% of diabetic cats increased number of lymphocytes were found, compared to only 5% of control cats. Only one diabetic cat had severe lymphocytic infiltration. However, β-cell and insulin antibodies have not been described in newly diagnosed diabetic cats so far [160].

Cats can also suffer from other specific types of diabetes mellitus, including loss of pancreatic islets due to pancreatitis, neoplasia, or other endocrinopathies. These cases of diabetes mellitus probably represent less than 20% of cases seen at primary care practices but may be overrepresented in referral practices [136]. At the time of diagnosis of DM, **pancreatitis** could be present in up to 60% of diabetic cats based on biochemical and imaging findings, even though clinical signs of pancreatic inflammation are uncommon [156-158]. When looking at the histological lesions, most of them are consistent with chronic pancreatitis, while acute or subacute necrotizing pancreatitis is a cause of mortality [159, 165]. Most of the time, pancreatitis is not sufficiently severe to cause feline DM but it may contribute to the loss of β-cells and thus decrease the chances for DM remission [165, 166]. Pancreatitis seems to be an infrequent cause of feline DM but seems to be a frequent comorbidity, and can occur during the course of the diabetic disease. Pancreatitis may also play a role in the development of diabetic ketoacidosis (DKA) [159, 167]. **Pancreatic adenocarcinoma** can also cause DM in cats, and is reported in 8-19% of feline DM patients euthanized in tertiary referral institutions [159, 168].

Insulin resistance and DM in cats can occur secondary to **hypersomatotropism** (also named acromegaly) or **hypercortisolism** (Cushing's syndrome) [145, 153, 162-164]. It is estimated that almost all cats suffering from hypersomatotropism and nearly 80% of cats with hypercortisolism will develop DM, which appears to be difficult to regulate because of the severe insulin resistance caused by the concurrent endocrinopathies [1]. Acromegaly typically begins clinically as poorly controlled DM, even with higher insulin doses [169, 170]. In the UK 25% of feline diabetes mellitus cases were estimated to be caused by acromegaly [171]. Progressive weight gain as well as higher bodyweights characterize acromegalic cats compared to non-acromegalic diabetic cats [171]. The link between feline DM and acromegaly will be further discussed in the next chapter which focuses on feline acromegaly. Regarding other endocrinopathies, hyperthyroidism and hyperaldosteronism are rarely associated with feline DM [1].

3.1.2 EPIDEMIOLOGY AND RISK FACTORS

Prevalence

Current estimates of the worldwide prevalence of feline DM are scarce. Data are either based on hospital records [43, 153, 172, 173], submissions to laboratory services [174] or insurance data [175, 176]. Estimates regarding the prevalence of feline DM vary from 0.25 to 1% [153, 172, 174, 175, 177]. Several studies from **Australia** and **UK** reported a prevalence for DM in cats at about 0.5% [172, 175, 178]. Another more recent study in the UK found a slightly higher prevalence of 0.58% of feline DM [12]. In **Sweden**, the prevalence of feline DM was estimated at about 0.21% [173]. The incidence rate of feline DM has been studied in this country and was evaluated at 11.6 cases per 10,000 CYAR (cat-years at risk) [176]. However, almost 30 years before this study, another report evaluated the incidence rate of feline DM at about 2.45 cases per 1,000 CYAR in North America, which reflects a higher incidence than in Sweden [177]. In the **USA**, the prevalence in veterinary teaching hospitals increased from 8 cases per 10,000 cats in 1970 to 124 per 10,000 in 1999 [153]. The authors suggested that this may reflect an increased willingness of pet owners to seek advanced veterinary care. Because cats of this study were mostly referred from private veterinary hospitals, this result may also reflect changes in referral patterns. It is not known whether this apparent increase in the feline DM prevalence is due to factors such as obesity becoming more common [153].

Risk factors

Risk factors associated with feline DM include **old age**, **male** gender, **obesity**, **physical inactivity**, **indoor confinement**, **breed**, repeated or long-acting **glucocorticoid** or **megestrol acetate administration** [153, 154, 175, 177]. Most of these factors decrease insulin sensitivity and increase the demand on β-cells to produce insulin [175-177].

Age, gender and neutering status:

In both humans and cats, increasing age has been associated with increased risk for DM. Juvenile onset of feline DM is a rare event. In the study of Prahl et al. (2007) involving 2576 diabetic cats in USA, only 1.3% were 1 year old or younger, 1.3% between 1 and 2 years old, whereas almost 50% of the cats were between 10 and 15 years old [153]. Others studies are in accordance with an increased risk of DM as patient age increases above 6 years old, with a peak incidence between 10 and 15 years of age [177, 178, 182]. In people, it has been shown that β-cell function deteriorates with age and insulin sensitivity declines, which are thought to

contribute to the increased risk of DM in older patients [183], and similar mechanisms may contribute to feline DM.

In cats, it has been shown that males are more prone to develop DM [153, 172, 175, 184]. However, in the study of O'Neill et al. (2016), although male cats showed 1.6 times the odds of DM compared with female cats in the univariable analysis, sex did not significantly contribute to a patient's risk of DM after accounting for the effects of other risk factors, including body weight in the multivariable analysis [182]. Male cats are more prone to obesity than females [179, 185] and some studies have also reported that male cats are more likely to develop hypersomatotropism, which can cause DM together with increasing bodyweight [186]. It is not yet clear if neutering in both sex is associated with an increased risk of DM. Neutering have been recognized as a risk factor for both sexes in some studies [153, 175, 177], although it did not remain a risk factor in some of their multivariable models [153, 175]. It has to be considered that neutering can lead to obesity, thereby increasing the risk to develop DM [153].

Obesity and insulin sensitivity:

It has been shown that obese cats are 3.9 times more like likely to develop DM than cats with an optimal weight [187]. The development of obesity in cats results in a 52% decrease in **insulin sensitivity** and reduced glucose effectiveness (the capacity of glucose to enhance its own cellular uptake and to suppress endogenous production) [179]. The insulin sensitivity is the ability of a given concentration of insulin to decrease blood glucose. Similar results were reported in another trial in which each kilogram increase in weight led to around 30% loss in insulin sensitivity [188]. Insulin sensitivity is not only decreased by **obesity**, but also by **physical inactivity** and by some **drugs**, such as glucocorticoids and progestins [175, 184-188]. **Reduced insulin sensitivity (or insulin resistance) is the key feature of T2DM**. Diabetic cats are about six times less sensitive to insulin than normal, causing an increased production of hepatic glucose, and a decreased glucose utilization in peripheral tissues [155, 193].

Breed predispositions:

Feldman et al. (2015) stated in their book that most of the diabetic cats are mixed-breed cats, such as Domestic Short-Hair and Domestic Long-Hair. Most studies investigating cat breeds as a potential risk factor for feline DM failed to identify other breeds than the Burmese breed as predisposed for developing DM. The **Burmese** cat breed has been reported at increased risk for DM in UK, Sweden, Australia, and New Zealand but not in USA [153, 172, 174, 175, 177, 194]. This geographical difference may be explained by the fact that European/Australian and

American Burmese breed lines have been kept separate since several decades and can be considered now to represent two different subpopulations, being genetically distinct from each other [195]. Burmese cats are being diagnosed for DM 4 times more than other cats, and studies revealed that about 10% of Burmese cats of 8 years of age or older suffer from DM [172].

When looking at studies investigating breed predispositions of cats for DM around the world, we observe some geographical differences. In **USA**, the Burmese has not been reported to be at risk for DM but the ***Main Coon***, the ***Russian Blue*** and the ***Siamese*** appear to be at risk for DM, although no OR have been calculated for these studies [194, 196]. In **Australia**, only the ***Burmese*** has been reported to be significantly at increased risk for DM [172, 174]. In the **UK**, O'Neill et al. (2016) reported 3 breeds at increased odds for DM: the ***Burmese*** (OR 3), the ***Norwegian Forest*** (OR 3.5) and the ***Tonkenese*** cats (OR 4.1) [182]. The Tonkinese breed was created in the 1950s through crossbreeding of Burmese cats, so according to the authors it is possible that this genetic similarity may have contributed to a shared predisposition for DM. In **Sweden**, the study of Öhlund et al. (2015) reported increased incidence rate ratios (IRR) of DM risk for the ***Burmese*** (IRR 4.3), the ***Russian Blue*** (IRR 3.8), the ***Norwegian Forest cat*** (IRR 1.9) and ***Abyssinian breeds*** (IRR 1.8) [176].

Genetic factors:

In cats, very little is known about the genetic background of DM pathogenesis. Regarding insulin sensitivity, although it is still unclear if it is genetically determined, lean cats with underlying low insulin sensitivity are at higher risk for developing glucose intolerance after gaining weight compared to cats with normal insulin sensitivity [179]. The heritability for feline DM has been investigated within the Burmese cat breeds. Heritability was estimated to be around 9%, and the genetics involved in this process appear to be autosomal rather than sex-related [172, 174, 175, 194, 197]. The study of Öhlund et al. (2015) supports this theory, reporting no sex predilection among Burmese cats. This breed appears to have a propensity for dysregulation in lipid metabolism, and lean Burmese cats demonstrate similar gene expression patterns to obese domestic cats [198]. Moreover, in overweight domestic shorthair cats with DM, the polymorphism in the melanocortin 4 receptor gene (Mc4R) is associated with DM, similarly to people [199]. This polymorphism was 3.7 times more likely in overweight DM cats versus overweight non-DM, although no difference was reported between obese and lean non-DM cats. Two very recent studies aimed to map the genetic basis of feline DM in Australian-bred Burmese cats [200, 201]. Both studies identified diabetes-associated haplotypes across several chromosomes. Mapping this condition in Burmese cats has revealed

a polygenic spectrum, implicating loci linked to pancreatic β-cell dysfunction, lipid dysregulation and insulin resistance in the pathogenesis of DM in Burmese cats [201].

3.1.3 CONCLUSION

Feline diabetes mellitus is a common endocrine disorder, which has seen its incidence increase over time. This may be explained by owners who are more inclined to take care of their pets' health, but also by an increase in the predisposing factors of this disease. Indeed, the change in lifestyle of domestic cats would be associated with obesity, more indoor and confinement and thus, increased risk for DM. Cats from several breeds displayed an increased risk for developing DM, with the Burmese breed being the most predisposed breed for DM. This is an indicator of a genetic influence that is just recently investigated in the past decade. However, probably DM in cats is a polygenic disease like in humans, and many genes may be associated with an increased risk for the disease.

3.2 FELINE HYPERSOMATOTROPISM – ACROMEGALY

3.2.1 CAUSES

Feline acromegaly, or hypersomatotropism (FeHS), results from chronic, excessive secretion of growth hormone in the adult animal. The anabolic effects of growth hormone (GH) are exerted through the intermediary hormone, insulin-like growth factor 1 (IGF-1), produced in the liver under the influence of GH. In most cats suffering from acromegaly, the cause is a neoplastic transformation of acidophils (somatotrophs) in the anterior pituitary (pituitary adenoma), leading to increased frequency and amplitude of the pulsatile secretion patterns of GH. In cats, these tumors grow slowly and may be present for a long time before clinical signs appear [202, 203]. Some cats also secrete other pituitary hormones in smaller amount and on rare occasions, cats may have double adenomas [204]. A small number of pituitary carcinomas and some non-neoplastic hyperplasia have also been described [170, 186].

Excess GH causes insulin resistance and subsequent DM by reducing insulin receptors, decreasing insulin receptor binding, and post-receptor insulin antagonism [186]. Aside from the peripheral action of GH on insulin, GH also has a direct action on pancreatic islet to increase β-cells secretory capacity and cause β-cell hyperplasia. In feline acromegaly, prolonged hypersomatotropism leads to DM, because insulin demand exceeds the secretory capacity [205].

3.2.2 EPIDEMIOLOGY AND RISK FACTORS

3.2.2.1 Prevalence

Although FeHS was thought to be an uncommon disease until recently, it is likely to be underdiagnosed. FeHS is indeed a relatively common underlying cause for feline DM. A few studies have determined the incidence of FeHS in the diabetic cat population, evaluating the potential increase of IGF-1 concentrations in blood samples of diabetic cats. Prevalence of FeHS have been estimated in a range from 18 to 32% with some differences in recruitment or screening methods [169, 186, 206]. The study of Schaefer et al. (2017) reported a prevalence of 21% in diabetic cats from the **Netherlands** and of 13% in diabetic cats from **Switzerland** [206]. In the **UK**, two other studies reported a prevalence of 18% and 32% of FeHS among the diabetic cat population studied [169, 186]. More recently, the same research group repeatedly found high IGF-1 levels in 27.3% of diabetic cats [170].

It has to be considered that all epidemiological studies evaluating the prevalence of FeHS among diabetic cats were based on the measurement of IGF-1 concentrations, and this measurement can lead to a certain rate of false-positive results [207, 208]. Moreover one study reported a diabetic cat population with high IGF-1 concentrations but without clinical features of FeHS [209]. A follow-up study showed that IGF-1 concentrations were significantly higher in diabetic cats receiving long-term insulin therapy (cats treated for over 14 months) than those who received short or medium term insulin therapy as well as healthy cats [210]. Thus, the length of insulin therapy also seems to play a role in IGF-1 concentrations in diabetic cats. False-negative IGF-1 results may also occur as hepatic IGF-1 synthesis is dependent on adequate concentrations of portal insulin, and such insulin can be deficient in newly diagnosed diabetic cats [211]. However until now, other diagnostic tools such as GH assays, GH suppression tests, alternative blood tests (such as serum ghrelin, a GH secretagogue), or imaging (CT scan or MRI) have not been demonstrated to be better diagnostic tools [136, 211].

Age, gender and body weight:

While GH deficiency appears to be a clinical concern only in kittens and young cats with growth issues, feline hypersomatotropism should be considered in any middle-aged to older cat with DM [136]. Most affected cats are 8 years and older, with an average of 10 to 11 years, with a range between 4 and 19 years old [170]. In the vast majority, Domestic Short-Haired and some Domestic Long-Haired are affected by acromegaly. There is a strong male sex predilection, as around 88% of cats affected were male (neutered or not) [170, 212]. As

described in the feline DM part, there is also a strong male predisposition for DM among cats. However, one study did not reported any sex predilection for FeHS [213].

Acromegalic cats weigh around 5 to 7 kg, with a range between 4 to 9 kg [1].

Genetic and environmental factors:

Regarding environmental factors that can contribute to the development of FeHS, one study investigated the role of organohalogenated contaminants (OHC) in acromegalic cats [214]. They reported a significantly higher OHC plasma concentrations in acromegalic cats as compared to cats with primary DM and those without an endocrinopathy. It was suggested that FeHS may reduce the cat's ability to metabolize persistent chemicals like environmental contaminants. Further research is needed to determine if there is a causal or consequential link with FeHS.

As for genetics, mutations of AIP (aryl-hydrocarbon-receptor interacting protein) gene, a tumor suppressor protein, has been demonstrated in people suffering from GH secreting adenomas [215]. AIP has a range of effects including activation of xenobiotic metabolizing enzymes, making the link between exposure and accumulation of OHCs even more interesting. One research group investigated the feline AIP gene, and reported that 4 of 16 cats with FeHS has a single non conservative SNP in exon 1 of the AIP gene, suggesting that some cats may be genetically predisposed to develop FeHS [216].

3.2.3 CONCLUSION

Over the last decade, FeHS has been increasingly recognized as a significant co-morbidity in feline DM. The prevalence of this disorder is far greater than that has been reported in the past. Thus, feline acromegaly is likely an underdiagnosed disease in older male cats, especially in cats with insulin-resistant DM. The diagnosis of FeHS is mainly made through IGF-1 measurements, although it can guide to misleading interpretations in the diagnosis. To make an accurate diagnosis, history, clinical signs, laboratory tests and advanced imaging should be used together. Nevertheless, the prevalence of hypersomatotropism seems sufficiently high to warrant its consideration when dealing with diabetic cats and particularly when problems with glycemic control arise. When the diagnosis of acromegaly is made in diabetic cats, the chances for diabetic remission, and the prognosis are worse.

3.3 *FELINE HYPERTHYROIDISM*

3.3.1 CAUSES

Since its first description in the veterinary literature only 35 years ago, hyperthyroidism (HET) has become the most common endocrine disorder of cats and one of the most important diseases in feline practice. HET is a clinical condition resulting from the overproduction and secretion of thyroxine (T4) and triiodothyronine (T3) by the thyroid gland. In the cat, this endocrinopathy is almost always the result of a primary autonomous condition of the thyroid gland. **Functional thyroid adenomatous hyperplasia** (or **benign adenoma**) involving one or both thyroid lobes is the most common pathologic change associated with feline HET, with more than 95% affected by one of this pathologic abnormality [213-215]. In approximately 70% of hyperthyroid cats, both lobes are affected, the disease is unilateral in the remaining 30% [217, 220]. Thyroid carcinoma is a rare cause of HET in cats, with less than 2% of hyperthyroid cats affected by this pathology, whereas it is the primary cause of HET in dogs [221].

Although great improvements have been made in the diagnosis and treatment of cats with HET, the underlying cause and pathogenesis of this disorder remains unclear, and have not been clearly elucidated. Initially, it was suggested that an immune-mediated cause is possible, and could be involved in the pathogenesis of HET in cats [222]. In people, Grave's disease is the most common cause of thyrotoxicosis, and is the result of circulating autoantibodies activating thyrotropin (TSH) receptors which, in turn, promote thyroid hormone production and secretion. However, no evidence of an immune-mediated cause was demonstrated in cats, whose HET is often considered analogous to human toxic nodular goiter [16, 223], having clinical and pathological similarities. They are both caused by adenomatous hyperplasia of the thyroid gland leading to the development of benign nodules secreting thyroid hormone autonomously, thus escaping control by the hypothalamus and pituitary gland [136].

3.3.2 EPIDEMIOLOGY AND RISK FACTORS

Prevalence

HET in cats was first described in 1979 and 1980 [218, 224, 225]. After these publications, it has emerged as the most common feline endocrinopathy and was accepted as the most important cause of morbidity in middle-aged cats in the USA [217, 226, 227] and the UK [228]. The prevalence in 1979 was around 0.3% and increased to 4.5% in 1985 (Scarlett et al., 1988). The age-specific hospital prevalence of feline HET in North America increased

significantly from 0.1 to 2% between 1978 and 1997 [229]. An increase in the hospital prevalence was also reported in Germany, where the number of affected cats increased from 0.2% in 1987-1994 to 2.6% in 1998 [230]. Some studies estimated the prevalence of HET in middle-aged and elderly cat populations. In Germany again, the hospital prevalence among cats over 8 years of age in a urban population was 11.4% in 2006 [231], and 10 years later it was reported at 12.3% in Southern Germany for another cat population of the same age [232]. Various prevalence estimates of the disease in North America and Europe indicate that the incidence of the HET appears to be increasing [229, 233, 234]. Because it is unlikely that improved diagnostic capabilities alone would account for such a dramatic increase in the prevalence of this disease, it is often suggested that HET may truly be a "new" disease of cats [217, 235]. Other factors may also explain this increased prevalence, such as an increased awareness of the condition by practitioners and pet owners and an increased longevity of cats.

Not only is there evidence for an increased worldwide prevalence of feline HET, but also for geographical variation in the prevalence of the disease [227]. Several studies have provided convincing evidence of genuine geographical variations. The disease is commonly seen in **USA**, **Canada**, **Australia**, **Europe**, **Japan** and **New Zealand** [213, 225, 227, 232-236], whereas it is much less commonly diagnosed and described in other areas, such as **Scandinavia** and **Hong-Kong** [241]. Moreover, Wakeling et al. (2005) reported a significant difference in the incidence rate for this disease in two different countries, with 11.92% in the **UK** versus 1.5% in **Spain**, in cats aged ***over 9 years of age*** [242]. In another study conducted in the **UK**, the prevalence of HET in cats aged 9 years or more was 7.8% [234], slightly lower than reported in cats of that age range in **Japan** (8.9%) [237], but higher than one other study conducted in **UK** reporting a prevalence of 6% [243]. More recently, the first study conducted in **South Africa** reported a prevalence of 7% of HET among cats of that age range [244]. Among cats ***10 years of age or older***, prevalence was reported at 8.66% in **UK** [234] which is much higher than reported in cats of that age range in **Hong-Kong** (3.93%) [245]. In **Ireland**, and more specifically in the greater Dublin area, the prevalence of hyperthyroid cats of 10 years of age or more is 21.1%, which considerably higher than reported in UK and Hong-Kong [246]. Among all the studies, the highest prevalence was reported in **Poland** with a prevalence of 20.14% of hypothyroid cats of ***7 years of age or more*** in 2014 [247]. In their report, Köhler et al. (2016) summarized the prevalence of feline HET recorded in different countries [232]. However, it is difficult to directly compare these results, because the studies used different case definitions (inclusion/exclusion criteria) and study populations.

Age, gender and neutering status:

The reported age range is 4 to 22 years with a mean age of 13 years, while the overall prevalence increased over the time, the mean age of onset has not changed between 1983 and 2004 [220, 226, 229]. Fewer than 5% of hyperthyroid cats are younger than 8 years of age [1].

Regarding sex predilection, some studies have reported increased odds of diagnosis of HET in females compared with males [229, 238], whereas others reported no sex predisposition for this disease [245, 248, 249]. There is limited evidence for neutering status as a risk factor for feline HET because many studies included only neutered cats or too few neutered cats to allow interpretation [229, 248]. Other reports did examine the influence of neutering on the risk to develop HET in cats but found no correlation [238, 247, 250]. However, this should be interpreted with caution because these studies included very few neutered cats so this may have resulted in a low power to detect association.

Breed predispositions:

The great majority of studies describing the epidemiology of feline HET did not report any breed predilection [1, 16, 136]. It has been reported that Siamese cats were at reduced odds of diagnosis with feline HET compared to non-Siamese [227], and that **Siamese** and **Himalayan** cats were at ***reduced odds*** compared to other breeds combined [250]. Purebred cats were also reported at reduced odds compared to non-purebred cats [232, 234, 238, 249]. However, De Wet et al. (2009) reported that domestic shorthair cats were at lower odds than other breeds in Hong-Kong [245]. A recent study described **Burmese, Persian** and **Siamese** cats at reduced risk of feline HET compared with non-purebred cats in England [234].

Genetic risk factors:

As several studies reported some feline breeds as being at lower risk to develop HET than other cats, this supports the idea of a possible genetic predisposition for HET. However, no investigation described the genetic background of these protected breeds so far. Moreover, mutations in the cAMP-activating G protein alpha subunit, as well as TSH receptor mutations have been identified in some hyperthyroid cats, although there are conflicting results about this last finding [251, 252]. G-proteins are normally involved in inhibition of a wide range of G-protein-dependent intracellular signaling processes, among which the signal for thyroid hormones secretion [253]. Decreases in inhibitory G proteins expression have been demonstrated in hyperthyroid cats, which may decrease the ability to inhibit cAMP production, which may result in an excess thyroid hormone secretion [253]. The role of this mutation in the pathogenesis of HET remains unclear.

Environmental risk factors:

Over the last 30 years, many studies have been performed to examine the cause of HET in cats. First identified possible risk factors were living strictly indoors and having exposure to lawn herbicides, fertilizers or pesticides, flea sprays, as well as feeding of canned cat foods [227]. The study of Kass et al. (1999) reported that cats eating a diet mostly composed of canned cat food were at 2 to 3-fold increased risk of developing HET, and 3-fold increase in risk for cats using cat litter [250]. Another study described that cats preferring fish or liver and giblets flavors of canned cat food had increased risk of disease, but that exposure to fertilizers, herbicides, pesticides, flea products and presence of a smoker in the home were not associated with an increased risk of disease [248]. In 2004, Edinboro et al. reported that feeding of pop-top canned cat food was associated with increased risk of developing HET. The same research team summarized the literature on risk factors for HET in 2010. Other possible risk factors included the consumption of baby food for kitten, the lack of iodine supplement in label ingredients, the increasing frequency of carpet cleaning and increasing years of exposure to well water and to gas fireplaces [254]. Thus, feline HET appears to be a multifactorial disease, with canned cat food identified as one of the major possible risk factors for this disease.

The iodine content in canned food for cats is very variable, some being deficient in iodine while others contain excessive amount of iodine [255]. The conclusion of the authors was that these dramatic variations in iodine intake may lead to development of nodular hyperplasia and eventually to clinical HET in the later stage. Furthermore, other factors appear to contribute to the pathogenesis of feline HET, such as the presence of soy isoflavones or the lack of Selenium in some commercial canned food that would lead to increased concentrations of tT4 and fT4 and decreased T3 in cats [256, 257]. Canned food may also contain goitrogens, compounds that can cause thyroid disruption because of a high degree of structural similarity to T4. Moreover, these molecules are mostly metabolized by glucuronidation, which is known to be a very slow process in cats [258]. **Bisphenol A (BPA)**, a known disrupter of the thyroid function, is used in pop-top cans in the manufacturing process and has been detected in 15 canned cat foods, with different level of contamination [259]. Among the different alterations of the thyroid function that BPA can cause, it can interfere with T3 binding that may lead to an increase in TSH secretion and eventually cause goiter [229]. **Polybrominated diphenyl ether (PBDEs)**, another known thyroid disrupter, can be found in canned food (especially in fish-flavored canned food) and in the cat's indoor environment, and has been suggested to play a role in the development of feline HET [260, 261]. PBDEs serve as flame retardants, and can be highly concentrated in house dust

because of their lipophilic properties, which will be ingested by cats during self-grooming. As for BPA, exposure to PBDEs can lead to chronic and excessive TSH secretion and thus eventually result in the development of adenomatous hyperplasia or neoplasia [260, 261]. However, an association between PBDEs and feline HET has yet to be proven.

3.3.3 CONCLUSION

Nowadays, feline HET is considered the most common endocrine disorder affecting cats, and its prevalence increased greatly over the last decades. This disease appears to affect cats at an older age, and no breed predisposition has been described so far. Several breeds such as Siamese, Himalayan, Burmese and Persian have been reported at reduced odds compared to other cats, suggesting that genetic factors may be involved in the pathogenesis of HET. Indeed, mutations of the TSH receptor gene or mutations of its associated G proteins seem to play an important role in the pathogenesis of this disease. Among all the studies investigating the potential risk factors for this disease, none of them have reported a single dominant factor involved in the development of feline HET. Rather, most of the studies described several risk factors, providing further evidence that HET is a multifactorial disease in cats. One of the most likely candidates playing an important causative role in the pathogenesis of HET in cats is one or more of the goitrogens (BPA and PBDEs) that have been found in canned food and in the cat's environment.

4 CONCLUSIONS

One of the main objectives of this literature review was to assess the epidemiology of the most encountered endocrinopathies in cats and dogs. The review of the literature in dogs showed that the prevalence of canine endocrinopathies appeared to be quite similar, with a prevalence of approximately 0.2% to 0.3% of HC, 0.2% to 0.8% of HOT and 0.3% to 0.36% of DM. Thus, regarding these data, HOT appears to be the most common canine endocrinopathy, followed by DM, and then HC. Some studies described the prevalence of these diseases among their study populations and a few reported the same pattern of prevalence for these endocrinopathies [13, 45], although one study in Brazil reported that HC was the most common endocrine disorder encountered, followed by DM and then by HOT [30]. When looking at how prevalence evolves over time, the prevalence of HC increased, as well as the prevalence of DM, although it is important to note in case of DM that the case-fatality rate decreased over time. As for endocrinopathies in cats, the prevalence of feline DM was estimated at around 0.25% to 1%, and

appears to increase with time. Regarding FeHS, although it was considered in the past as a rare endocrine disorder in cats, it is now considered that 18% to 32% of diabetic cats are suffering from FeHS. HET was first described in 1979 and became the most common endocrinopathy in cats over time worldwide, although one study in Brazil reported feline DM as the most commonly seen endocrinopathy in cats, followed by hyperthyroidism [30]. However, the study population is certainly too small to allow robust conclusions on the epidemiology of cat diseases in Brazil.

There is thus some strong evidence for increasing occurrence of canine HC, canine and feline DM, FeHS and feline HET in the literature, confirming the hypothesis mentioned in the introduction about the increased prevalence of the overproduction endocrinopathies. Several factors can explain the rise of these endocrinopathies. The life expectancy of pets increased over the last decades, and there is a greater awareness of these diseases as well as better diagnostic tools for the diagnosis of these complex diseases. Moreover, neutering being more and more frequent, it may also contribute to the increased occurrence of DM in male dogs and cats. Obesity is also more common in dogs and cats, predisposing them as well to DM, through different pathogenesis. Finally, it is important to mention the importance of environmental risk factors when considering the increased occurrence of HET in cats. The exposure to lawn and flea control products outdoor, as well as goitrogens (such as PBDEs and BPA) present in the cat's indoor environment and in canned food were often reported as predisposing factors for feline HET.

As for the hypothesis that the prevalence of canine HOT may have decreased over time due to better diagnostic tools avoiding false positives, this review could not demonstrate this. Indeed, although this endocrinopathy appears to be the most frequently reported in dogs, studies interested the epidemiological features of canine HOT are very sparse, the different population size as well as the use of various diagnostic methods between studies make the comparison too difficult, and do not allow any conclusion about the evolution of this disease over time.

This literature review also investigated breed predispositions to these endocrinopathies in the world and allowed to observe that there are predisposed breeds at different levels of risk for the 3 canine endocrinopathies and for feline DM. Protected breeds have been reported for canine HC, canine DM and feline HET. Not only interbreed differences were observed but also intrabreed differences according to geographical regions. It may be explained by the fact that various breeds are overrepresented in some countries while absent or rarely encountered in others. There may also be intrabreed genetic differences between regions of the world. This second theory is supported by several studies which revealed intrabreed variation of the prevalence of certain haplotypes related to some diseases [90, 91, 262].

One of the difficulties encountered when evaluating risk factors for these diseases was the lack of control group in certain studies, especially regarding the frequency of breeds in the general population. This problem was particularly apparent in the analysis of breed predisposition to canine HC and HOT, which made the interpretation of these data difficult. Moreover, the lack of detailed methods in various studies as well as the use of different inclusion/exclusion criteria, or different diagnostic methods, also complicated the comparisons.

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