A THESIS FOR THE DEGREE OF MASTER

# A Retrospective Study of Clinical Relevance Between Cholestatic Disease and Pituitary Dependent Hyperadrenocorticism in Dogs

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# Abstract

## A Retrospective Study of Clinical Correlation between Cholestatic Disease and Pituitary Dependent Hyperadrenocorticism in Dogs

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A high prevalence of cholestatic disease, including gall bladder mucoceles (GBM), in naturally occurring canine pituitary-dependent hyperadrenocorticism (PDH) patients has been reported. A clinical correlation between cholestatic disease and PDH management is insufficiently identified. There can be significant differences in not only the clinical features of PDH due to concurrent cholestatic disease, but also regarding the management of PDH with trilostane, owing to the water-insolubility of trilostane. Sixty five client-owned dogs with naturally

occurring PDH were included. Each dog was treated with trilostane for at least 3 months prior to this study, and exhibited a “good clinical response”, as determined by owners. Statistical comparisons of clinical signs, routine blood tests, basal and post-ACTH (Adrenocorticotrophic hormone) cortisol concentration, and “optimal trilostane dosage” were made after the dogs were separated into the following 3 groups through ultrasonographic imaging: control group, cholestasis group, and GBM group. Comparisons were also analyzed pertaining to each dog’s sex.

Seventy two percent (n = 47) of whole patients turned out to have cholestasis or GBM. The GBM group had not only more severe clinical signs, but also a significantly different total cholesterol (T-Chol) and post-ACTH stimulation test value at the time of diagnosis. There was a tendency ($P$ = 0.057) and significance ($P$ = 0.003) of a high prevalence of cholestatic disease in females and dogs that weighed under 6 kg, respectively. The ‘optimal dosage’ (kg/mg/day) of the GBM group and the cholestasis group was 2.5 and 1.5 times that the dosage of the control group, respectively ($P$ = 0.000). There was a tendency ($P$ = 0.112) of a low proportion of hypercholesterolemia in female group.

This study suggests that gall bladder disease associated with cholestatic disease is closely correlated with canine PDH, related to both clinical features and drug management. Furthermore, those findings may be related to hypercholesterolemia, a female predisposition, and the water-insoluble characteristic of trilostane.

**Key words:** Hyperadrenocorticism, Mucocele, Cholesterol, Trilostane, Female

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# 1. Introduction

Hyperadrenocorticism (HAC) is one of the most common endocrine diseases of dogs, and is characterized by the overproduction of cortisol. HAC is classified as pituitary-dependent-hyperadrenocorticism (PDH), adrenal-dependent hyperadrenocorticism (ADH), or iatrogenic depending on the origin of cortisol[1-3]. HAC is characterized by variable clinical signs and several medical complications that develop secondary to a prolonged excess of cortisol. The well-described complications include systemic hypertension, pancreatitis, diabetes mellitus, steroid hepatopathy, pulmonary thromboembolism, pituitary macrotumor syndrome, and etc[1-8]. PDH patients can be treated with medication, surgical procedures, radiation therapy, or combination of these options[3,9-12].

Trilostane (Vetoryl®, Dechra) is a medication that is now used worldwide in HAC dogs since its development as a veterinary product in 1998[12-16]. It is a competitive inhibitor of 3β-hydroxysteroid dehydrogenase, thereby decreasing the synthesis of glucocorticoids, mineralocorticoids, and adrenal androgens. Trilostane management should be started with a relatively low dose, and followed with periodic monitoring to evaluate

effectiveness, which is based on clinical signs, routine blood testing, and an adrenocortical function test[12,16]. PDH patients can take trilostane once daily (SID) or twice daily (BID). Some studies suggest BID might result in a better clinical response than SID, and one study suggests that there is no statistical difference of the daily mean dosage between SID and BID treatment intervals[16-18]. However, the individual 'optimal dosage' is not easily predictable before the initiation of treatment and the range of dosages is widely distributed[14,18,19].

GBM, which is defined as an abnormal and immobile accumulation of mucin accompanied by hyperplasia of mucus-secreting gall bladder epithelium[20-22], have been suggested as having a possible association with multiple endocrinopathies, especially HAC[21,23,24]. MLL Mesich et al. reported that GBM is highly prevalent in HAC in an age- and breed-matched case-control study, showing that the prevalence of GBM in dogs with HAC was 29 times greater than in dogs without HAC[24]. However, the association between HAC and cholestatic disease is less clear. According to FS Pike *et al.,* only 23% of mucocele patients had HAC. In addition, the correlation of clinical features, pathophysiology, and management of cholestatic disease, including GBM, in dogs with PDH has not yet been clarified.

This study aims to determine the correlation between clinical features, pathophysiology, and management between cholestatic disease, including GBM, and PDH in dogs. It is showed that canine PDH patients with cholestatic disease not only have more severe clinical signs and clinicopathologic findings but also require a higher trilostane dosage and a longer stabilizing period than control patients. This study also suggested that there may be a pathophysiologic etiology with sex relation and cholesterol.

# 2. Material and Methods

## *2.1. Study population*

In this case-controlled retrospective study, at first, 103 privately owned dogs with naturally occurring PDH that had visited the Veterinary Medical Teaching hospital (Seoul National University, Seoul, South Korea) from 2010 to 2014 were selected. Diagnosis of HAC was made on the basis of the dog's history, physical examination, results of routine blood testing, and endocrine function test results. The endocrine tests that were used to obtain a diagnosis were as followings: ACTH (Adrenocorticotrophic hormone) stimulation test, low-dose dexamethasone suppression test (LDDST), and urinary cortisol:creatinine ratio (UCCR)[3,25-27]. All patients underwent abdominal radiography and ultrasonographic examination at the time of diagnosis, some patients were also evaluated using computed tomography (CT) scanning. Of the 103 PDH-diagnosed patients, the patients that were managed at a local hospital after diagnosis or were not followed-up with appropriately were excluded. The remaining 65 patients were followed-up with until they were exhibiting a "good clinical response." as determined by the owner, with a post-ACTH stimulation value being 2.0-9.1 μg/dL. This is

the criteria for a proper post-ACTH cortisol concentration according to the trilostane manufacturer's data sheet.

The patients with appropriate follow-up and response to therapy were divided into 3 groups: Group 1 (control group, n = 18), no evidence of cholestasis in the gall bladder. Group 2 (cholestasis group, n = 32) had evidence of cholestasis or cholelithiasis but no immovable sludge. Group 3 (GBM group, n=15) had GBM with evidence of immovable sludge within the gall bladder[21,22,27-31].

### *2.2. Diagnostic tests*

A thorough history and physical examination to determine clinical signs and presenting signs were performed in all dogs. A complete blood cell count (CBC), urinalysis, and routine biochemical profile including alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT) were performed in all dogs. Triglyceride (TG) and total cholesterol (T-Chol) tests were performed in 40 patients, 83% (n = 15) of the control group, 78% (n = 25) of the cholestasis group, 93% (n=14) of the GBM group, respectively. ACTH stimulation tests were

performed in all dogs (100%), and in addition in some cases, an LDDST (n = 22) or an UCCR (n = 2) or both also were performed. The diagnosis was confirmed if the result of LDDST or ACTH stimulation test was adequate along with sufficient clinical signs. To perform the ACTH stimulation test, cortisol concentrations were measured before and 1 hour after IV or IM administration of 5 μg/kg synthetic tetracosactrin. The diagnosis was considered pertinent to HAC when the post-ACTH value of cortisol concentration was ≥20 μg/dL. For the LDDST, serum samples were collected before, 4 hours, and 8 hours after administration of 0.01 mg/kg IV dexamethasone. A cortisol concentration >1.4 μg/dL in the sample collected at 8 hours was considered compatible with HAC. To perform the UCCR, a first morning urine sample was collected at home at least 2 days after a visit to our hospital, and a diagnosis of hyperadrenocorticism was determined by finding an increased UCCR (>60 × 10-6). Serum cortisol concentrations from collected samples were measured using a chemiluminescence system, validated for use in the dog. The UCCR was used as additional test with ACTH stimulation test or LDDST[3,25-27].

### *2.3. Ultrasonographic evaluation*

A thorough ultrasonographic exam of the entire abdomen was performed in all patients in the radiology department of same hospital at the time of diagnosis.

The differentiation of PDH was based on ultrasonographic features of the adrenal gland and, additionally in some cases, on the results of the LDDST and HDDST. Patients had any suspicion of an adrenal tumor (AT) in the sonographic exam were excluded from this study. The findings of AT-suspicion included moderate asymmetry (diameter of larger gland > 2 cm), contralateral adrenocortical atrophy (smaller adrenal width < 5 mm), destruction of normal tissue architecture, acoustic shadowing, and hyperechoic foci of an enlarged gland, or some combination of these findings. Patients with cortisol suppression (<1.4 μg/dL or <50% of basal cortisol concentration) at 4 hours (LDDST) were considered to have PDH[25,32].

After excluding adrenal-dependent patients, we divided the remaining patients into 3 groups depending on the sonographic findings of the gall bladder. The control group had no evidence of biliary stasis, with an assumed normal-sized gall bladder lumen. The cholestasis group had evidence of mobile gall bladder sludge or calculi with a dilated gall bladder

lumen. All patients in this group were defined as not having characteristics of a mucocele, which was evaluated by repositioning the patient and using gentle transducer agitation on the ventral abdomen to suspend the gall bladder sediment. The GBM group exhibited immobile sludge and a finely stellate or striated pattern within the gall bladder lumen[21,22,30,31,33-35].

### *2.4. Treatment and follow-up*

All patients in this study were treated SID or BID with trilostane. The percentage of SID and BID treated patients were as follows: Group 1 (56% and 44%), Group 2 (34% and 66%), Group 3 (21% and 79%). The initial dosage ranged between 1.0 and 5.0 mg/kg/day.

Owners were requested to bring patients for re-evaluation at 14 days and 1 month after treatment began. After 1 month, evaluation schedules of each patient were variable, depending on the clinical response and endocrine test results of the previous recheck, and were schedule in at-least 2 week intervals. In this study, 41 of 65 patients had a third recheck at 6 weeks after treatment began, while 24 of 65 patients had a third recheck at 2 months after treatment began. Once patients achieved a good clinical response and

proper Post-ACTH cortisol concentration, the interval of the recheck schedule was adjusted to at least every month. At each re-evaluation, all owners were asked about the clinical response since the time of diagnosis. The owners also were questioned about the presence of any potential adverse effects from trilostane treatment such as anorexia, weakness, vomiting, or diarrhea, irrespective of whether these signs could be attributable to the medication[12,14-16,18]. All dogs were physically examined and a serum biochemical profile and ACTH stimulation test were performed. The ACTH stimulation tests were performed in all groups at the first re-evaluation, between 4 and 6 hours after the administration of prescribed trilostane. The range of post-ACTH cortisol concentrations that were regarded as an indication of "proper disease control" was 2.0-5.4 μg/dL, or 5.4-9.1 μg/dL with a good clinical response determined by the owner. These criteria for proper post-ACTH cortisol concentrations followed the trilostane manufacturer's data sheet.

The dosage of trilostane was regulated individually based on post-ACTH cortisol concentrations and clinical signs. The trilostane dosage was retained in dogs with "good clinical response" and an ACTH stimulation test with a result below 9.1 μg/dL. The dosage of trilostane was reduced by 25% to 50% in dogs with a post-ACTH cortisol concentration lower than 2.0 μg/dL, regardless of the presence or absence of adverse effects. All

patients in this study were followed-up for at least one more month after achieving “proper disease control” as mentioned above.

### *2.5 Statistical Analysis*

Results were analyzed by a SPSS statistical package (version 23). The population features of all 3 groups were compared by a chi-squared test, Fisher’s exact test, or linear by linear association test for categorical data, and population attributes treated as continuous data were compared by a Levene *t*-test, Mann-Whitney test, or ANOVA. Linear correlations were calculated by Spearman’s nonparametric correlations. Differences were considered significant at values of $P \leq 0.05$.

# 3. Results

## *3.1. Signalments*

The sex, breed, mean age, body weight and body condition score (BCS) of each group are summarized in Table 1. Twenty-nine dogs were male (5 intact, 24 neutered) and thirty-six (14 intact, 22 spayed) dogs were female. The most frequently represented breeds were Shih Tzu (22%; n = 14), Miniature Schnauzer (15%; n = 10), Yorkshire Terrier (15%; n = 10), Maltese (14%; n = 9), mixed breed (11%; n = 7), Poodle (5%, n = 3), and Pomeranian (5%, n = 3). There were 2 Cocker Spaniels, 2 Miniature Pinschers, 2 Dachshunds, 2 Boston Terriers, and 1 Pekinese. The age at diagnosis ranged from 6 to 17 years (mean ± SD: 10.7 ± 2.3) and the body weight ranged from 1.5 to 18.0 kg (mean ± SD: 6.4 ± 3.3). The BCS ranged from 4/9 to 8/9 (mean ± SD: 6.2 ± 1.1). There were no statistical differences in age (P = 0.682) and body condition score (P = 0.797) among the 3 groups. There was a certain statistical difference (P = 0.003) in body weight between the control group (mean ± SD: 8.2 ± 3.4) and the other population, while no statistical difference (P = 0.501) between cholestasis group (mean ± SD: 5.9 ± 3.4) and GBM group (mean ± SD: 5.1 ± 1.7) was present. There was a tendency (P = 0.057) of a female predisposition. The portion of

female patients was 39% (n = 7) in the control group, 56% (n = 18) in the cholestasis group, and 73% (n = 11) in the GBM group, respectively. These results suggest a tendency of females and breed predispositions in groups having GB lesions.

### *3.2. Clinical signs in the GBM group and female group*

The most common clinical signs were polyuria, polydipsia, abdominal distension, alopecia, and lethargy. In the control group, 89% (n = 16) of dogs presented with polyuria and polydipsia, 61% (n = 11) with abdominal distension, 50% (n = 9) with alopecia, and 44% (n = 8) with lethargy. In the cholestasis group, 91% (n = 29) of the dogs presented with polyuria and polydipsia, 69% (n = 22) with abdominal distension, 56% (n = 18) with alopecia, and 47% (n = 15) with lethargy. In the GBM group, 93% (n = 14) of the dogs presented with polyuria and polydipsia, 93% (n = 14) with abdominal distension, 87% (n = 13) with alopecia, and 80% (n = 12) with lethargy. There was no statistical differences among groups with regard to the presence of polyuria and polydipsia (P = 1.000). There were significant statistical differences between the GBM group and every other group regarding the presence of abdominal distension (versus group 1, P = 0.046;

versus group 2, P = 0.078), alopecia (versus group 1, P = 0.026; versus group 2, P = 0.040), and lethargy (versus group 1, P = 0.037; versus group 2, P = 0.032) while there no statistical differences between the control group and the cholestasis group. The odds ratios for clinical signs in the GBM group are presented in Table 2.

The most common clinical signs mentioned in previous paragraph were statistically analyzed according to sex. In the male group, 90% (n = 26) of the dogs presented with polyuria and polydipsia, 62% (n = 18) with abdominal distention, 48% (n = 14) with alopecia, and 45% (n = 13) with lethargy. In the female group, 92% (n = 33) of the dogs presented with polyuria and polydipsia, 81% (n = 29) with abdominal distention, 72% (n = 26) with alopecia, and 61% (n = 22) with lethargy. There was a significant statistical difference between the male group and the female group regarding the presence of alopecia (P = 0.049, OR 2.79, 95% CI; 0.99-7.81) and there were no statistical differences regarding the presence of polyuria and polydipsia (P = 1.000), abdominal distention (P = 0.098) and lethargy (P = 0.191).

### *3.3. Routine blood tests*

The hematological test results, urinalysis results, ALT, AST, ALP and TG at diagnosis were similar among the 3 groups and there were no statistical differences in any variables after statistical analyses were performed. The portion of GGT-elevated dogs was 56% (n = 10) in the control group, 66% (n = 21) in the cholestasis group, and 93% (n = 14) in group 3. There was a significant statistical difference (P = 0.024) in the GGT-elevation proportion among the 3 groups by linear by linear association. The portion of T-chol elevated dogs was 40% (n = 6) in group 1, 63% (n = 15) in group 2, and 93% (n = 13) in group 3. There was a significant statistical difference (P = 0.003) in T-chol elevation proportion among the 3 groups by linear by linear association. The bar graphs of serum chemistry results are presented in Figure 1.

The proportion of hypertriglyceridemic or hypercholesterolemic patients were also statistically analyzed based on sex and neutered status. There were no statistical differences in TG elevated proportion between the whole male group and the whole female group. There was a significant statistical difference (P = 0.024) in T-chol elevated proportion between non-GBM male patients and non-GBM female patients while there was no statistical difference (P = 0.133) between whole male patients and whole female patients. The odds ratios for these analyses are presented in Table 3.

The mean ± SD (range) of serum T-chol and TG of patients were statistically analyzed based on neutered status in female group. The mean ± SD (range) of serum T-chol of patients were 316 ± 99 mg/dL (193-710) in the intact female group, 406 ± 155 mg/dL (194-526) in the spayed female group. The mean value (range) of serum TG of patients were 139 mg/dL (68-315; median, 103) in the intact female group, 246 mg/dL (106-785; median, 199) in the spayed female group. There was a tendency (P = 0.086) and statistical difference (P = 0.049) in high serum T-chol concentrations and high serum TG concentrations in spayed female group, respectively. These analysis are presented in Table 4.

### *3.4. Cortisol concentrations*

The mean ± SD (range) of basal cortisol concentrations of patients were 7.6 ± 5.0 μg/dL (2.0-20.1) in the control group, 7.5 ± 4.5 μg/dL (1.5-16.8) in the cholestasis group, 10.2 ± 4.9 μg/dL (3.2-20.2) in the GBM group. There was no significant statistical difference (P = 0.154) in basal cortisol concentrations among the 3 groups. The mean value (range) of post-ACTH cortisol concentrations of patients were, 31.0 μg/dL (16.1-50.0; median, 32.2) in the control group, 34.9 μg/dL (12.4-50.0; median, 33.9) in

the cholestasis group, and 39.9 μg/dL (24.6-50.0; median, 40.2) in the GBM group. There was a significant statistical difference (P = 0.030) between the GBM group and the remaining dogs, while no statistical difference (P = 0.489) was found between the control group and the cholestasis group. The box plot of basal cortisol concentration and post-ACTH cortisol concentration is presented in Figure 2.

### *3.5. Most common ultrasonographic findings*

In all groups, the most common findings during abdominal sonographic evaluations were hepatomegaly (85%, n = 55), gall bladder lesions (72%, n = 47), urinary bladder lesions (54%, n = 35), hepatic nodules (49%, n = 32), and pancreatic lesions (40%, n = 26). There were no statistical differences among the 3 groups concerning these lesions. The urinary bladder lesions are included thickened and irregular walls, irregular bladder margins, or hyperechoic material within the lumen. The pancreatic lesions included a heterogenous echotexture, edematous change, and hyperechoic or hypoechoic changes.

### *3.6. Initial and optimal dosage of trilostane*

The mean value (range) of initial trilostane dosage was, 2.1 mg/kg/day (1.0-5.0; median, 2.0) in the control group, 2.0 mg/kg/day (1.0-5.0; median, 2.0) in the cholestasis group, and 2.9 mg/kg/day (1.0-5.0; median, 2.0) in the GBM group. The most frequent doses were 1 BID (mg/kg, 34%, n = 22), 2 SID (mg/kg, 20%, n = 13), 1 SID (mg/kg, 18%, n = 12) and 2 BID (mg/kg, 12%, n = 8). The decision of the initial trilostane dosage was made after a subjective assessment of each patient. There was a statistical difference (P = 0.022) between the GBM group and the other groups, and no statistical difference was found between the control group and the cholestasis group.

The mean ± SD (range) of the "optimal trilostane dosage" of patients was 3.1 ± 1.3 mg/kg/day (1.0-6.0; median, 3.0) in the control group, 4.6 ± 1.7 mg/kg/day (2.0-8.0; median, 4.5) in cholestasis group, and 7.8 ± 2.3 mg/kg/day (4.0-11.5; median, 7.0) in the GBM group. There was a significant statistical difference (P = 0.000) among the 3 groups.

# 4. Discussion

This study showed that a pronounced association exists between PDH and cholestatic disease with regard to not only clinical features and clinicopathologic findings but also trilostane management. Cholestatic disease, including GBM, needs to be considered as a crucial complication of PDH in regards to major clinical signs and cortisol elevation. This finding was supported by other data within this study, including odds ratios of major clinical signs in the GBM group, and a higher post-ACTH cortisol concentration of GBM group. The pathophysiology of GBM occurrence in PDH patients can be associated with cholesterol metabolism and a female sex predisposition, and there might be a tendency of breed predisposition. Furthermore, we found that PDH dogs with cholestatic disease require higher trilostane dosages than those with no cholestatic lesions.

Several previous studies suggested various GBM risk factors, including dysmotility of the gallbladder, cholelithiasis, cholecystitis, mucus hypersecretion, hyperlipidemia, or hypercholesterolemia, endocrine disease, genetic factor and breed predisposition[21-23,30,34,36-38]. However, the precise etiology has not been definitively identified.

Shetland Sheepdogs, Cocker Spaniels and Miniature Schnauzers are known by their predisposition to GBM until now. Meanwhile, PDH tends to occur in smaller dogs; approximately 75% of PDH dogs weigh less than 20 kg. In our study, 100% of dogs weighed less than 20 kg and 63 of 65 dogs are toy to small breeds. The body weight (kg) of the control group is significantly higher than that of the cholestasis group and the GBM group while the BCS of the 3 groups are almost equal. Assuming a cut-off value as a risk factor is under 6 kg, only 17% (n = 3) of the control group weighed less than 6 kg while 56% (n = 18) of the cholestasis group and 67% (n = 10) of the GBM group weighed less than 6 kg. In addition, there was a strong statistical association (P = 0.003) among the 3 groups by linear by linear association. This result suggested that there might be numerous, uninvestigated, specific breed predispositions of cholestatic disease in PDH dogs. An insertion mutation of ABCB4 in various canine breeds affected with GBM were reported. Otherwise, in humans, a number of genes related to gall stone formation have been identified. Those gene proteins include ABCB4, ABCB11, ABCG5/G8, ARDB3, APOA1, APOB, and CCK1R[39-43], and they are in charge of the biliary secretion of phospholipid and cholesterol, gall bladder hypomotility, bile salt synthesis, and so on. In this study, there are a total of 10 Yorkshire Terriers and 9 Malteses in the whole population while only 1 Yorkshire Terrier and no Maltese belong to the

control group. Otherwise, 8 of 14 Shi-tzus and 3 of 10 Miniature Schnauzers belonged to the control group. Although not stated in the results, Maltese (P = 0.007) and Yorkshire Terrier (Odds ratio; 12.00, CI 1.18-122.27, P = 0.033) with PDH have statistically significant higher prevalence of cholestatic disease than Shih-tzus with PDH. There are no statistical differences of sex, age, BCS, neutered or spayed status among these 3 breeds. This result suggests that the further study of risky gene involvement is needed.

In humans, gallstone and gallbladder polyps are the most common gall bladder diseases, whereas GBM is considered as a rare condition. Human Gallstone diseases have variable risks and genetic factors including pregnancy, childbirth, female sex, certain race, acute weight loss, estrogen therapy and obesity. Female predisposition is due to hormonal effects, including bile cholesterol hypersaturation and gall bladder dysmotility that are induced by estrogen and progesterone, respectively. The formation of cholesterol gallstones starts with cholesterol-supersaturated bile. The cholesterol crystals are snared in mucin, which induce gall bladder wall dysfunction, and eventually stone formation[41-45]. In addition, cholesterol-supersaturated bile gradually induces mucus hypersecretion, which is one of the principal mechanisms that contribute to gallstone formation[41-43,46]. Moreover, an inverse correlation to serum high-density lipoprotein (HDL)

cholesterol is well known in human medicine[39-43,47-49]. All these findings are also diversely investigated in laboratory animals[46,50-53].

In canines, a significant correlation between GBM and hyperlipidemia has been reported, while limited information about specific lipoproteins of GBM dogs is available[54]. One study reported that a decreased amount of plasma HDL cholesterol during experimental cholestasis in dogs[55]. Our study showed that sex-cholesterol relation might exist in GBM dogs with PDH. There were significant linear by linear correlations between hypercholesterolemia and the development of cholestatic disease while a tendency of female predisposition of cholestatic progression with PDH. A high hypercholesterolemia prevalence (93%) within the GBM group is thought to have two major causes, and those are dysregulated lipid metabolism by hypercortisolism and decreased bile excretion of cholesterol by GBM[1-3,31,54,56]. Bile excretion is the prime pathway of cholesterol elimination from body[56-58]. It was reported that the gall bladder ejection fraction is significantly decreased in dogs with gall bladder sludge or GBM in one study[31]. In our study, although female dogs were thought to have more decreased bile excretion ability than male dogs due to having more severe cholestatic progression, it was presented that there was a lower hypercholesterolemia proportion in females than that in males, with a statistical significance in non-GBM patients.

This information and these results suggest a theory explaining the progression of cholestatic disease in dogs with PDH. Hypercortisolism with PDH provides a "sufficient serum cholesterol pool" by dysregulated lipid metabolism. Then female PDH patients can uptake overflowing cholesterol easily to the gall bladder through the hormonal actions of estrogens, and as a result, it can lead to mucus hypersecretion. Furthermore, progesterone also significantly impairs emptying and motility of the gallbladder[49,52,59,60]. The increase in plasma estrogen and progesterone concentrations in ferrets with HAC was reported[61]. Otherwise, there was no significant increase of plasma estradiol concentrations in HAC dogs, while there was significant increase of progesterone and androstenedione[62,63]. This theory may also provide a clue for higher odds ratio of GBM dogs with HAC than that with hypothyroidism, which was reported in one study[24]. In that study, the odds of GBM in dogs with hypothyroidism were 3 times higher than without hypothyroidism, while the odds with HAC were 29 times higher. Although hypothyroid dogs can also provide "sufficient serum cholesterol pool", they may have decreased and down-regulated plasma estrogen and progesterone concentrations[64-67]. As a result, hypothyroid dogs may have a relatively mild effect of raising cholesterol hyper-saturation and dysmotility of the gall bladder despite enough cholesterol in their plasma. Undoubtedly, there would be more various pathophysiologic reasons of higher odds ratio of

HAC than that of hypothyroidism, and further studies are required.

Trilostane is well known for its lipid-soluble character. Therefore, it is strongly recommended to administer this medicine with or after meals, which can stimulate bile excretion from gall bladder[12-15,68]. It is also well known that GBM dogs have a potential risk of lipid-soluble nutrition deficiency due to extra hepatic biliary obstruction[69-71]. High "optimal trilostane dosage" of the GBM group in this study can be explained by two causes. The first is the higher cortisol production of the GBM group than that of other groups, which is likely induced by advanced PDH progression. This is supported by a higher post-ACTH cortisol concentration than the other groups, however there are no significant differences of basal cortisol concentrations among the 3 groups. The second is a decreased ability of bile excretion induced by concurrent cholestatic disease[21,31,33]. It is thought that the severity of PDH progression may be not enough to explain the high trilostane dosage in the GBM group. These results suggest the occurrence of cholestatic disease can be a major reason of wide distribution of "optimal trilostane dosage" of HAC patients. Consequently, proper client education is required when treating PDH patients with cholestatic disease, especially GBM. Meanwhile, we attempted to find completely resolved cases of GBM after treatment initiation, which is based on a study about nonsurgical resolution of GBM dogs[72]. However, regrettably, there are no completely

resolved cases, but 4 of 15 GBM patients have had partial improvement in an ultrasonographic gall bladder exam after 6 months of GBM and PDH management. Moreover, only 1 of 4 had a decreased dosage of trilostane, which is not sufficient for analysis.

The present study includes a number of considerations and limitations. The first was the small number of the study population and the nature of retrospective study, which limits more reliance that can sited on not enough strong significance. To the author’s knowledge, no specific GBM animal model existed until now, which make difficulties in performing a prospective study. As descripted previously, TG and T-chol tests were performed in only 83% (n = 54) of patients. However, there was still a tendency (P = 0.055) of female predisposition in 54 patients. About serum cortisol measurement, It was only 50 μg/dL that the upper limit of available measurement in our machine was set, and which made a number of patients (n = 13) met the upper cap of post-ACTH cortisol concentration. About 11% (n = 2) of control group, 19% (n = 6) of cholestasis group, and 33% (n = 5) of GBM group equally presented 50 μg/dL of post-ACTH cortisol concentrations, and we could not if and how much further elevation occurred. It might be more statistically significant even between control group and cholestasis group if no limited measurement of cortisol

concentrations were available. The second was a biased breed distribution. In Korea, toy breeds and small breeds are generally more popular than medium to large breeds, and preference of some specific breeds is remarkable. However, this is not a limitation of this study because it made us focus and revealed a tendency of breed predisposition.

# 5. Conclusion

This study suggests that GBM is a crucial complication of PDH going along with the severity of hypercortisolism. PDH dogs with GBM have more severe clinical signs and higher post-ACTH cortisol concentrations than those without GBM. The pathophysiology of GBM formation with PDH may include breed, genetic, and female sex predisposition, which may be associated with cholesterol metabolism through bile excretion. In addition, there is a significant difference in the required trilostane dosage, which is likely due to the lipid-soluble characteristic of trilostane. It is recommended that cautious monitoring and proper client education about the risk of cholestasis and GBM formation be performed.

**Table 1. Demographic characteristics of the study population**

| | Gall bladder lesion | | |
|---|---|---|---|
| | Control | Cholestasis | GBM |
| n (65) | 18 | 32 | 15 |
| Age (years) | 11.1 ± 2.2 | 10.5 ± 2.3 | 10.7 ± 2.3 |
| Sex* | M(11), F(7) | M(14), F(18) | M(4), F(11) |
| BW (kg)** | 8.2 ± 3.4 | 5.9 ± 3.4 | 5.1 ± 1.7 |
| BCS (9-pt) | 6.2 ± 1.0 | 6.2 ± 1.1 | 6.0 ± 1.1 |
| Breeds | | | |
| Shih-Tzu | 8 | 4 | 2 |
| Miniature Schnauzer | 3 | 6 | 1 |
| Yorkshire Terrier | 1 | 6 | 3 |
| Maltese | | 6 | 3 |
| Mixed breed | 1 | 5 | 1 |
| Poodle | | 1 | 2 |
| Pomeranian | | 2 | 1 |
| Cocker Spaniel | 2 | | |
| Miniature Pinscher | | 2 | |
| Dachshund | | | 2 |
| Boston Terrier | 2 | | |
| Pekinese | 1 | | |

All data are presented with the mean value (±SD).

BW, body weight; BCS, body condition score; M, male; F, female

* P = 0.057; ** statistically significant difference: P = 0.003

**Table 2. Odds ratio for PU/PD, abdominal distention, lethargy and alopecia in the gall bladder mucocele (GBM) group against the other group**

| Clinical signs | Number | Chi-square test | Odds ratio | 95% CI | P |
|---|---|---|---|---|---|
| PU/PD | 14/15 | VS Control | 1.75 | 0.14-21.43 | 1.000 |
| | | VS Cholestasis | 1.45 | 0.14-15.21 | 1.000 |
| Abdominal distention | 14/15 | VS Control | 8.91* | 0.95-83.62 | 0.046 |
| | | VS Cholestasis | 6.36 | 0.73-55.30 | 0.078 |
| Alopecia | 13/15 | VS Control | 6.50* | 1.13-37.48 | 0.026 |
| | | VS Cholestasis | 5.01* | 0.98-26.18 | 0.040 |
| Lethargy | 12/15 | VS control | 5.00* | 1.04-24.03 | 0.037 |
| | | VS cholestasis | 4.53* | 1.07-19.19 | 0.032 |

* Statistically significant difference: $P < 0.05$.

PU/PD, polyuria and polydipsia; VS, versus; CI, confidence interval

**Table 3. Odds ratio for hypertriglyceridemia and hypercholesterolemia in the female group**

| Factor | Whole patients | | Non-GBM patients (Control + cholestasis) | |
|---|---|---|---|---|
| | HyperTG | HyperT-chol | HyperTG | HyperT-chol |
| Male | 19/22 (86%) | 17/22 (77%) | 17/19 (89%) | 14/19 (74%) |
| Female | 23/32 (72%) | 18/32 (56%) | 14/21 (67%) | 8/21 (38%) |
| OR | 0.40 | 0.38 | 0.24 | 0.22 |
| 95% CI | 0.10-1.71 | 0.11-1.28 | 0.04-1.32 | 0.06-0.85 |
| P | 0.208 | 0.112 | 0.133 | 0.024* |

* Statistically significant difference: $P < 0.05$.

OR, Odds Ratio; CI, confidence interval; HyperTG, Hypertriglyceridemia; HyperT-chol, Hypercholesterolemia

**Table 4. Odds ratio of hypertriglyceridemia and hypercholesterole mia in intact group and mean value of TG (mg/dL) and T-chol (mg/dL) of intact and spayed female group**

| | Mean TG | HyperTG | Mean T-chol | HyperT-chol |
|---|---|---|---|---|
| Intact | 139 ± 79 | 6/12 (50%) | 316 ± 99 | 5/12 (42%) |
| Neutered | 246 ± 165 | 15/20 (75%) | 406 ± 155 | 12/20 (60%) |
| OR | - | 0.33 | - | 0.48 |
| 95% CI | - | 0.07-1.52 | - | 0.11-2.04 |
| P | 0.049* | 0.250 | 0.086 | 0.314 |

* Statistically significant difference: $P < 0.05$.

OR, Odds Ratio; CI, confidence interval; HyperTG, Hypertriglyceridemia; HyperT-chol, Hypercholesterolemia

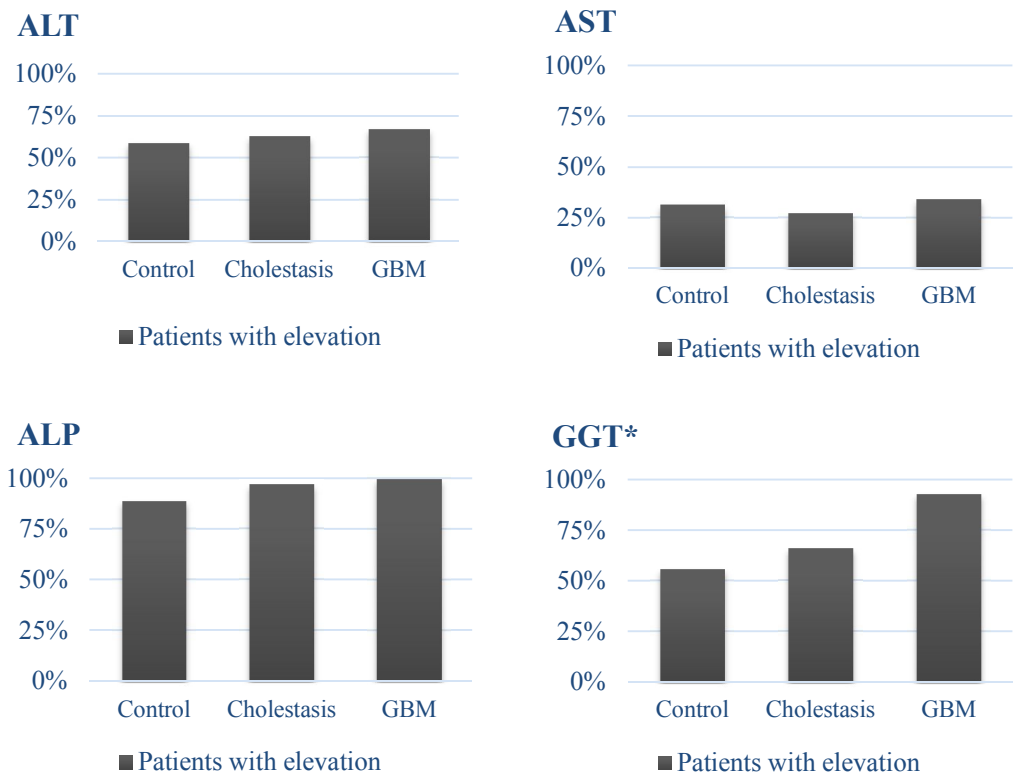


**Figure1. Elevated proportion of selected serum liver enzyme profiles of each group.** * statistically significant difference: $P < 0.05$.

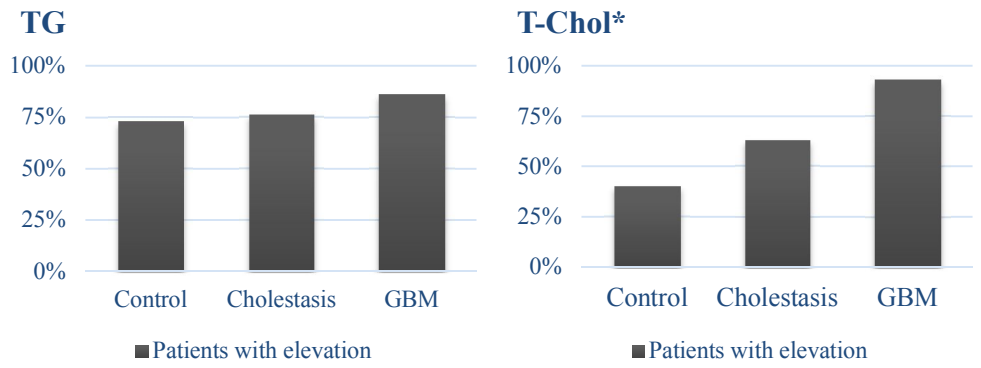


**Figure 2. Elevated proportion of serum triglyceride and total cholesterol of each groups.** * Statistically significant difference: $P < 0.05$.

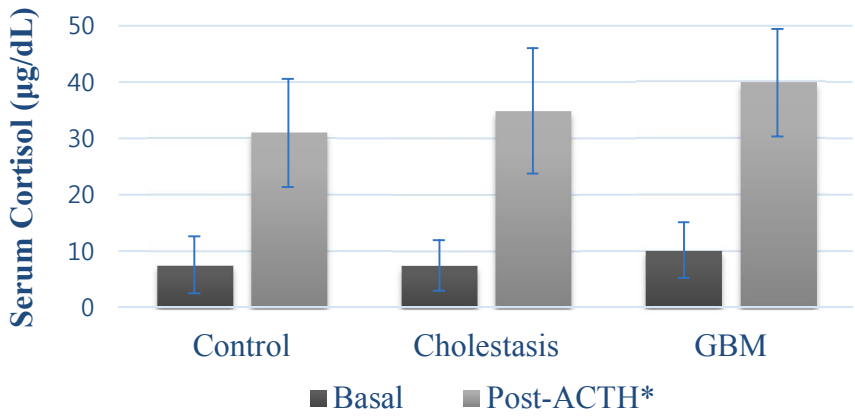


**Figure 3. Comparison of serum cortisol level among 3 groups.** Statistically significant difference; * $P = 0.03$

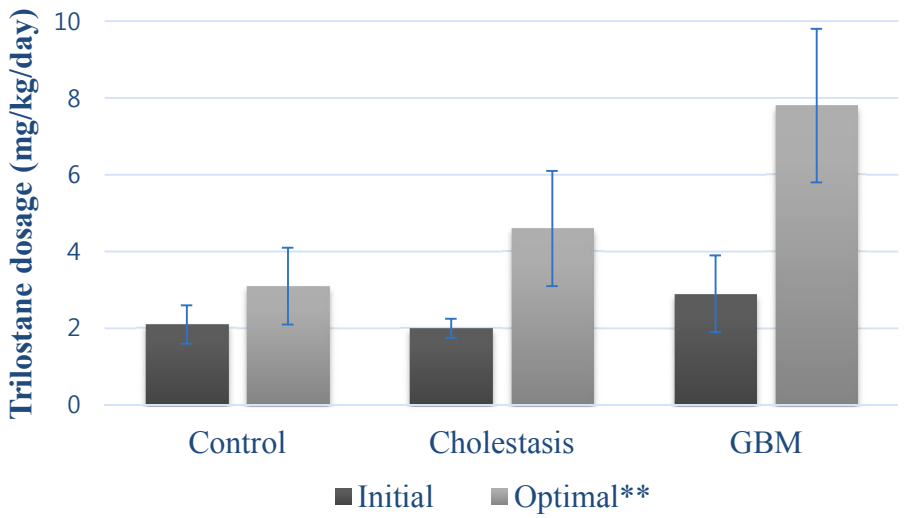


**Figure 4. Comparison of required trilostane dosage among 3 groups.** Statistically significant difference; ** $P = 0.000$.

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# 국문 초록

# 개 뇌하수체 의존성 쿠싱 환자에서 담즙 정체성 질병과의 임상적 연관성에 대한 후향적 연구

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개에서 가장 흔한 내분비 질병 중 하나인 뇌하수체 의존성 부신피질 기능항진증(PDH) 환자에서, 담낭 점액종을 포함한 담즙 정체성 질병의 높은 유병률은 잘 알려져 있다. 본 연구는 특히 체중 20 kg 이하의 개 PDH 환자 담즙 정체성 질병과의 임상적

연관성을 알아보기 위한 후향적 연구이다. 2010년 1월부터 2014년 6월까지 서울대학교 동물병원에서 치료받고 있는 65마리의 개 PDH 환자를 대상으로 진행하였다. 모든 환자는 본 연구에 앞서 트릴로스탄으로 3개월 이상 관리되었으며, 보호자에 의해 결정된 “양호한 약물반응”을 보인 환자만 선정되었다. 해당 환자들은 복부 초음파 영상검사 결과에 따라 대조군, 담즙정체군, 담낭 점액종군의 세 군으로 분류되었다. 임상증상, 주요 혈청화학검사, 부신피질호르몬 자극검사 전후의 코르티솔 농도, ‘안정기 트릴로스탄 용량’ 등의 통계적 분석을 실시하였다. 이상의 분석들은 성별에 따라서도 실시되었다. 전체 환자의 72% 가 초음파상 담즙정체 혹은 담낭점액종 소견을 보이는 것으로 나타났다. 담낭 점액종군의 환자들은 임상증상뿐 아니라, 총콜레스테롤 및 부신피질호르몬 자극검사 후의 코르티솔 농도에서 유의적인 차이가 나타났다. 암컷군에서 담즙정체성 질병의 높은 선형관계 경향이 나타났으며, 6 kg 이하 환자들에서는 뚜렷한 담즙정체성 질병의 위험도 증가가 나타났다. 담즙정체군과 담낭 점액종군의 ‘안정기 트릴로스탄 용량’은 대조군에 비해 각각 2.5 배 및 1.5 배로 뚜렷한 차이가 나타났다. 또한, 암컷 그룹에서 고콜레스테롤혈증 환자 비율의 낮은 경향성이 나타났으며, 그 경향성은 담

낭 점액종군을 제외한 환자군에서는 더욱 뚜렷하게 나타났다. 이러한 결과들은 임상적 특징뿐 아니라 약물 관리에 있어서도 개 PDH 와 담즙정체성 질병이 밀접한 관련이 있음을 제시한다. 추가적으로, 이러한 결과들은 고콜레스테롤혈증, 암컷의 성별 소인, 트릴로스탄의 불용성에 따른 결과로 생각된다. 따라서, 특히 한국의 임상 환경에서 개 쿠싱 환자들에 대한 담즙정체성 질병에 대한 면밀한 감시와 고콜레스테롤혈증 개선에 대한 노력이 필요할 것으로 생각된다.

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**주요어**: 쿠싱; 점액종; 트릴로스탄; 암컷; 콜레스테롤

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