

# Serum Leptin and Ghrelin Levels and Their Relationship with Serum Cortisol, Thyroid Hormones, Lipids, Homocysteine and Folic Acid in Dogs with Compulsive Tail Chasing

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Article Code: KVFD-2016-16334 Received: 13.06.2016 Accepted: 30.08.2016 Published Online: 06.09.2016

## Citation of This Article

**Yalcin E, Yilmaz Z, Ozarda Y:** Serum leptin and ghrelin levels and their relationship with serum cortisol, thyroid hormones, lipids, homocysteine and folic acid in dogs with compulsive tail chasing. *Kafkas Univ Vet Fak Derg*, 23 (2): 227-232, 2017. DOI: 10.9775/kvfd.2016.16334

## Abstract

The aim of this study was to investigate serum leptin and ghrelin levels and their relations with circulating cortisol, thyroid hormones, lipids, homocysteine (Hcy) and folic acid in dogs with compulsive tail chasing (CTC). The material of this study consists of fifteen dogs with CTC and 15 healthy controls of various weights, breeds, ages of both sexes were enrolled in the study. CTC was diagnosed on the basis of the dog's behavioral history, clinical signs, and results of other medical assessments. None of the dogs were considered to have concurrent medical disease that would account for CTC. Dogs with CTC had a higher leptin ( $8.3 \pm 0.9$  ng/mL vs  $1.7 \pm 0.2$  ng/mL,  $P < 0.001$ ) and lower ghrelin levels ( $74 \pm 7$  pg/mL vs  $144 \pm 41$  pg/mL,  $P < 0.05$ ) than those of healthy controls. Serum cortisol, lipids (cholesterol, phospholipids and NEFA) and Hcy levels increased ( $P < 0.05$ ), whereas serum folic acid decreased ( $P < 0.001$ ) in dogs with CTC as compared with controls. Serum ghrelin correlated negatively with cholesterol ( $P < 0.05$ ), but serum leptin correlated positively with cholesterol, fT4, and phospholipids ( $P < 0.05$ ). These results suggest that serum leptin and ghrelin levels may bring up a new perspective on our understanding of the pathophysiological mechanisms associated with CTC. Serum levels of both hormones may be associated with serum levels of lipids and free T4.

**Keywords:** *Leptin, Ghrelin, Thyroid hormones, Lipids, Tail chasing, Dog*

## Kompulsif Kuyruk Isıran Köpeklerin Serum Leptin ve Ghrelin Seviyeleri ve Serum Kortizol, Tiroid Hormonları, Lipidler, Homosistein ve Folik Asit İle İlişkileri

## Özet

Bu çalışmanın amacı, kompulsif kuyruk ısırık köpeklerde serum leptin ve ghrelin seviyeleri ve sirküle eden kortizol, tiroid hormonları, lipidler, homosistein (Hcy) ve folik asit arasındaki ilişkiyi araştırmaktır. Çeşitli ağırlık, ırk, yaş ve her iki cinsiyetten 15 kuyruk ısırık ve kontrol grubu olarak 15 sağlıklı köpek çalışmaya dahil edildi. Kuyruk ısırık tanısı, davranış anamnez formu, klinik bulgular ve diğer medikal değerlendirmelerin sonuçlarına göre konuldu. Kompulsif kuyruk ısırık köpeklerin hiçbirinde eşlik eden başka bir medikal hastalık bulunmamaktaydı. Kompulsif kuyruk ısırık köpekler, kontrol grubundaki köpeklere göre yüksek leptin ( $8.3 \pm 0.9$  ng/mL vs  $1.7 \pm 0.2$  ng/mL,  $P < 0.001$ ) ve düşük ghrelin ( $74 \pm 7$  pg/mL vs  $144 \pm 41$  pg/mL,  $P < 0.05$ ) seviyesine sahipti. Kontrol grubu ile karşılaştırıldığında kompulsif kuyruk ısırık köpeklerin serum kortizol, lipid (kolesterol, fosfolipidler ve NEFA) ve Hcy seviyesi artmış ( $P < 0.05$ ), bunun aksine serum folik asit seviyesi ( $P < 0.001$ ) azalmıştır. Serum ghrelin seviyesi, kolesterol ( $P < 0.05$ ) ile negatif korelasyon gösterirken, serum leptin seviyesi, kolesterol, fT4 ve fosfolipidler ( $P < 0.05$ ) ile pozitif korelasyon göstermekteydi. Sonuçlar değerlendirildiğinde, serum leptin ve ghrelin seviyelerindeki değişikliklerin kompulsif kuyruk ısırık patofizyolojik mekanizmasını anlamak için yeni bir perspektif getireceği düşünülmektedir. Her iki hormon da serum lipid seviyeleri ve serbest T4 düzeyi ile ilişkili olabilir.

**Anahtar sözcükler:** *Leptin, Ghrelin, Tiroid hormonları, Lipidler, Kompulsif kuyruk ısırık, Köpek*

## INTRODUCTION

Obsessive compulsive disorder (OCD) is a neuro-psychiatric disorder in humans and animals. Canine

compulsive disorder includes excessive tail chasing, light/shadow chasing and flank sucking <sup>[1-3]</sup>. Clinical and neuro-biological similarities between dogs and humans with OCD were reported <sup>[3,4]</sup>. Thus, canine compulsive behaviors



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such as compulsive tail chasing (CTC) have been suggested as a promising model for human OCD [3].

Human and canine OCD have been associated with a biochemical disturbance at the level of neurotransmitter systems [1] and activation of hypothalamic-pituitary-adrenal (HPA) system [5,6]. Compulsive disorders are also known to be stress responsive and compulsive symptoms increase at times of stress [6,7]. Serum cortisol level as an indicator of activated HPA system is used to describe the presence of stress in humans [8], dogs [9], and cats [10].

Leptin and ghrelin are two hormones related with energy balance. Leptin, an anorexigenic hormone, is a mediator of long-term regulation of energy balance, suppressing food intake and thereby resulting in weight loss. Ghrelin, an orexigenic hormone, is playing a role in meal initiation [11]. Recently, leptin and ghrelin hormones have also been correlated in the pathophysiology of stress [12]. Leptin inhibits and ghrelin facilitates neuroendocrine stress responses in rats [12]. Hypercortisolemia increases serum levels of leptin and decreases serum levels of ghrelin in dogs. As serum levels of leptin and ghrelin are affected by cortisol [13], it is possible to hypothesize that these hormones might play a role in the regulation of stress response in dogs with OCD.

Current literature shows that some psychiatric disorders in humans might be related to the serum levels of folate and homocysteine (Hcy) [14-16], lipids [17,18] and thyroid function [19]. Thyroid status is considered as an important determinant of the serum level of total Hcy [20] and lipids (cholesterol, lipoproteins, etc.) in humans [17,18,21,22]. There is also one study indicating a relationship between serum level of lipid (serum cholesterol elevations) and OCD in dogs [23]. Based on the accumulated evidence, we hypothesized that circulating leptin, ghrelin, folate, Hcy, lipids and thyroid hormones might have a role in dogs with OCD. Thus, in this study, to understand of pathophysiological mechanism of OCD, we investigated serum leptin and ghrelin levels and their relations with circulating thyroid hormones, folate, Hcy, lipids, and cortisol in dogs with CTC.

## MATERIAL and METHODS

### Dogs

This study was performed on 15 healthy dogs and 15 dogs with CTC that were referred to the Small Animal Clinics Internal Medicine Department, Faculty of Veterinary Medicine, Uludag University, Bursa, Turkey in January-July 2016. Dogs with CTC were 10-35 kg (mean 27.2 kg±1.5 kg), and of various breeds (3 Anatolian shepherd dogs, 3 German shepherd dogs, 3 Golden retrievers, 3 mixed breeds, 1 Terriers, 1 Doberman, 1 Labrador retriever), sex (11 males, 4 females) and age (8 months-9 years, mean 3.3±0.7 years) were evaluated. Dogs (n=15), which were referred for vaccination purposes, were also enrolled in

the study as control after the consent of the owners and on the basis of normal physical examination results and complete blood count. Control dogs were of various weights (23.5±1.5 kg), mixed breeds of either sex (10 males, 5 females), and ranged from 12-96 months (34±2.5 months) in age. No significant differences were observed between the two groups regarding the aforementioned parameters. The body condition score for each dog was evaluated by using a 5-point scale (1: thin, 2: underweight, 3: ideal, 4: overweight and 5: obese) [24]. All experiments conducted by us in this study were performed in line with ethical approval from the ethical committee of University (16/1-5).

### Diagnostic Procedures

A behavioural diagnosis was made for each dog on the basis of the dog's behavioural history, clinical signs, and results of other medical assessments, as published in the previous studies [23,25]. Dogs were assessed for seizure disorder, opioid-mediated stereotypy, local vasculitis or neuritis, anal sac diseases and pruritus. None of the dogs were considered to have concurrent medical disease (such as dermatological disease, vector-borne diseases, and renal diseases) that would account for CTC. Behavioral history included age at onset, frequency and duration of bouts since onset, general history, and current or previous medical conditions. All owners reported that their dogs commonly whined, barked, or growled during tail chasing. In this study, affected dogs had to have tail chasing bouts for a minimum of 60 s/bout at least 3 times/d during the previous two months in order to be included into the study.

### Sample Collection and Measurements

Venous blood samples were collected, after a fasting period of 12-16 h, from cephalic veins into vacutainer tubes with or without EDTA (Becton Dickinson, Temse, Belgium) for complete blood count (Cell Dyne 3500R, Abbott, Germany) and serum biochemistry panel (Aeroset, Abbott), respectively. All dogs were screened for common vector-borne diseases (anaplasmosis, borreliosis, dirofilariosis, ehrlichiosis, and leishmaniosis) by speed tests (Bionote, Anigen, South Korea), and dogs sero-positive for vector-borne pathogens were excluded from the study.

Serum leptin and ghrelin levels were measured by radioimmunoassay (RIA) using a commercially available kit (Multispecies leptin RIA kit and active ghrelin RIA kit, Linco Research, St. Charles, MO). Validity and reliability of these RIA kits for measuring serum leptin and ghrelin levels in dog were determined in our previous studies [13,26]. Since active ghrelin is too unstable to be measured in stored samples [27] and acidification of plasma prevents rapid desacylation of ghrelin [28], 1 N hydrogen chloride was added to serum samples before freezing [13]. Serum cortisol was measured by a solid-phase chemiluminescent enzyme immunoassay system (Immulite 2000, BioDPC, Los

Angees, CA) as reported earlier [26].

Serum samples were tested for total thyroxin ( $T_4$ ), free  $T_4$  ( $fT_4$ ), triiodothyronine ( $T_3$ ), and free  $T_3$  ( $fT_3$ ) concentrations. Hormone analysis was performed by RIA techniques (Advia Centaur™) as reported earlier [29].

Serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C) and triglycerides levels were measured by an automated clinical chemistry analyzer (Architect ci8200; Abbott GmbH Co KG, Wiesbaden, Germany) using commercially available assay kits (Abbott GmbH Co KG). Low-density lipoprotein cholesterol (LDL-C) concentrations were calculated using the formula:

$$\text{LDL-C (in milligrams per deciliter)} = \text{total cholesterol} - (\text{HDL} - \text{C} + \text{triglyceride}/5).$$

Serum non-esterified fatty acid (NEFA) concentration was measured using a commercially available enzymatic colorimetric assay kit (Wako Chemicals, Neuss, Germany) [30]. Serum phospholipids were measured by an enzymatic colorimetric method using a commercially available assay kit (Wako Chemicals), which have been reported as choline-containing phospholipids (in milligrams per deciliter) [30].

### Statistical Analysis

Data were analysed statistically by two-group comparison student t test (SigmaStat GmbH, Erkrath) and expressed as mean±SEM. Pearson's correlation analysis was used to determine a relationship between the mean levels of serum leptin, ghrelin, cortisol, Hcy, folate, lipids, and thyroid hormones. A *P* value of <0.05 was considered significant.

## RESULTS

Routine clinical and hematological findings were within reference limits in all healthy dogs (data not shown). Dogs with CTC had a higher mean body condition score ( $4.2 \pm 0.6$ ;  $P < 0.001$ ) than controls ( $3.2 \pm 0.4$ ).

Dogs with CTC had a higher leptin ( $8.3 \pm 0.9$  ng/mL vs  $1.7 \pm 0.2$  ng/mL,  $P < 0.001$ ) and lower ghrelin levels ( $74 \pm 7$  pg/mL vs  $144 \pm 41$  pg/mL,  $P < 0.05$ ) than those of healthy controls (Table 1).

Serum cortisol, lipids (cholesterol, phospholipids and NEFA) and Hcy levels increased ( $P < 0.05$ ), whereas serum folic acid decreased ( $P < 0.001$ ) in dogs with CTC as compared with controls. There were no statistically significant differences on serum thyroid hormones (except  $fT_3$ ) between the groups studied. Serum  $fT_3$  level in dogs with CTC was higher ( $P < 0.05$ ) than that of controls (Table 2).

Serum ghrelin correlated negatively with cholesterol

**Table 1.** Serum levels of leptin, ghrelin, lipids, thyroid hormones, homocysteine and folic acid in healthy dogs and dogs with compulsive tail chasing (CTC)

Parameters	CTC Mean±SEM	Healthy Controls Mean±SEM	P Value
Leptin ng/mL	8.36±0.90	1.70±0.26	=<0.001
Ghrelin pg/mL	74.94±7.29	144.11±41.41	= 0.029
T. Cholesterol mg/dL	203.42±16.03	140.40±10.85	NS
HDL mg/dL	73.00±11.09	89.88±7.26	NS
LDL mg/dL	128.11±11.99	32.44±3.25	=<0.001
VLDL mg/dL	15.94±1.87	12.50±1.28	NS
Tg mg/dL	79.63±9.42	58.75±5.28	NS
Phospholipid mg/dL	338.16±17.05	276.11±14.60	=0.027
Nefa mg/dL	1.74±0.17	0.85±0.15	=0.002
TT <sub>4</sub> µg/dL	1.79±0.09	1.91±0.14	NS
fT <sub>4</sub> ng/dL	0.72±0.10	0.48±0.02	=0.072
TT <sub>3</sub> ng/mL	0.44±0.03	0.34±0.03	NS
fT <sub>3</sub> pg/mL	1.87±0.15	1.34±0.10	=0.03
Hcy µmol/L	11.52±0.84	6.29±0.23	=<0.001
Folic acide ng/mL	3.25±0.32	6.41±0.56	=<0.001

( $P < 0.05$ ) and serum leptin correlated positively with cholesterol,  $fT_4$ , and phospholipids ( $P < 0.05$ ). There was a negative correlation ( $P < 0.05$ ) between changes in serum ghrelin and leptin levels in healthy controls.

## DISCUSSION

This study showed that serum leptin levels were higher and ghrelin levels were lower in CTC dogs when compared with the healthy counterparts [26]. Increased serum leptin and decreased ghrelin levels and their correlation with circulating thyroid hormones and lipids in dogs with CTC provide further information to understand the pathophysiology of OCD, and to develop new treatment strategies for these patients.

In the present study, CTC, one of the most common forms of OCD in dogs, was diagnosed as reported earlier [23,25]. Serum leptin concentrations ( $1.7 \pm 0.2$  ng/mL), measured by RIA in healthy dogs, were slightly lower than those of healthy dogs in the previous studies:  $2.5 \pm 0.1$  ng/mL [13],  $2.4 \pm 0.1$  ng/mL [26], and  $2.3 \pm 0.5$  ng/mL [31]. This difference may be explained by diurnal rhythms of circulating leptin as well as using different measurement methods (RIA or ELISA) and kits (multi-species or canine specific leptin) [31]. In this study, no noticeable influence of age, gender, and breed on serum leptin levels was observed as reported by Ishioka et al. [32].

In this study, dogs with CTC had higher leptin ( $8.3 \pm 0.9$  ng/mL) and lower ghrelin levels ( $74 \pm 7$  pg/mL) than those of healthy controls, indicating a possible association between leptin and ghrelin systems and psychogenic disorders

**Table 2.** Serum levels of leptin and ghrelin and their relations with serum lipids, thyroid hormones

Parameters	T. Cholesterol	HDL	LDL	ft4	Phospholipids
Leptin	r: 0.600 P<0.05	NS	NS	r: 0.634 P<0.05	r: 0.643 P<0.05
Ghrelin	r: -0.477 P<0.05	r: -0.512 P<0.05	r: - 0.462 P<0.05	NS	NS

as well as a good inverse correlation between them. The results of serum leptin in this study showed similarity to those of a human study [33], in which serum leptin level was slightly higher (but not statistically significant) in the OCD group than in the healthy control group. High body condition score, observed in dogs with CTC, may enhance the serum leptin concentration by increasing leptin secretion from adipose tissue [24,32,34].

Since active form of ghrelin as compared with total ghrelin is essential in particular for biological [28] and endocrine activities [35], and thus, is physiologically more crucial in terms of OCD [36], active ghrelin measurements were chosen in the present study. Observed serum ghrelin level (144±41 pg/mL) in healthy dogs was in good accordance with the levels of 172±17 pg/mL and 117±42 pg/mL reported for healthy beagle dogs [37] and humans [38], respectively. As compared to healthy controls, serum ghrelin levels in dogs with CTC were found lower in this study, whereas Atmaca et al. [39] and Emül et al. [33] reported a trend of higher ghrelin levels in patients with OCD. These differences of serum ghrelin between the studies might have resulted from the presence of depressive disorders in patients with OCD [33,39].

In this study, elevated levels of serum cortisol, as compared to control dogs, were thought to be associated with the HPA axis activation in dogs with CTC, in concordance with the results in patients with OCD [6]. In the previous studies, in addition to serum cortisol elevation, hyperactivity of HPA axis, the main mammalian system of stress response [6], was confirmed by increased corticotropin-releasing hormone levels in cerebrospinal fluid [40] and increased urinary cortisol levels in patients with OCD [41]. Elevated serum cortisol has been accepted as a physiological marker of stress and behavior abnormalities, particularly for dogs in animal shelter, as well [42].

Our observations on serum lipid profile confirmed and expanded the findings of the previous studies [23,43] reporting that dogs with CTC had significantly higher total cholesterol and LDL-cholesterol compared with control dogs, by demonstrating the increasing serum phospholipids and NEFA in dogs studied. The findings of this study were very similar to those of a previous study [23]; VLDL-cholesterol and triglyceride levels did not differ significantly between the groups. Similar to studies of dogs, elevated cholesterol [44], LDL- and VLDL-cholesterols and triglyceride levels were observed in human OCD patients compared with the control subjects [18]. In agreement with earlier studies in dogs [23,43] and humans [17,18], our observations

confirm that serum lipid profile might be changed in dogs suffering from CTC.

On the other hand, a significant increase in serum phospholipid and NEFA brings up a new perspective which may help explain, at least in part, pathophysiological mechanisms associated with OCDs, such as CTC in dogs. Because phosphatidylcholine, as a primary phospholipid, is found at higher levels in myelin, cell membranes and brain parenchyma [45], it may have a crucial role for development of neuropsychiatric disorders in dogs as in humans [45]. In addition, excessive serum levels of NEFA, as observed in the present study, were reported to enhance oxidative stress [46] leading to several neuropsychiatric diseases including OCD [47]. Brain tissue has a high percentage of phospholipids that can easily be peroxidized. Recently, markers of oxidative stress and free radical induced injury to the brain tissues in OCD patients were reported, as well.

In this study, of thyroid hormones, only serum ft3 levels was found to be significantly higher in dogs with CTC than in controls, in accordance with euthyroid syndrome, most probably due to increased tissue metabolic demands in response to CTC as a non-thyroidal illness in dogs studied. One previous study [48] showed that basal values of thyroid hormones and thyroid stimulating hormone were normal in patients with OCD, and another study [19] reported that higher rates of panic disorder, OCD, and major depressive disorder were observed in thyroid patients than in the general population. Aizenberg et al. [49] underlined that dysregulation of the hypothalamic-pituitary-thyroid axis in OCD patients. Our results did not confirm the results arising from human studies indicating that altered levels of thyroid hormones might be associated with pathophysiology or maintenance of OCD.

Since serum Hcy has been considered as a sensitive marker for folate deficiency and they have important roles in carbon transfer metabolism (methylation) [16,39], in this study serum Hcy and folate levels were evaluated together. Our results of serum Hcy (6.2±0.2 µmol/L) and folate levels (6.4±0.5 ng/mL) in healthy dogs were in good accordance with those of the previous studies in dogs (5.1-10.9 µmol/L and 4.2-7.5 µg/L, respectively) [50] and humans (8.1±2.2 µmol/L and 7.5±1.9 ng/mL, respectively) [16]. In this study, serum Hcy levels increased (11±0.8 µmol/L), and serum folic acid decreased (3.2±0.3 ng/mL) in sick dogs, indicating the presence of hyperhomocysteinemia and serum folate deficiency in dogs with CTC. These results were very similar to the human studies on OCD [16,39]. It is well known that elevated serum Hcy and decreased folate

are associated with poor cognitive function and some psychiatric disorders. These results can be explained by the importance for the production of serotonin as well as for other monoamine neurotransmitters and catecholamines. Observations on the antidepressant effects of folate supplementation may support the importance of these nutrients in psychopathology<sup>[16]</sup>.

In the present study, based on the correlation studies, it may be speculated that serum leptin and ghrelin might have a role to regulate circulating lipids (total cholesterol, HDL-C, LDL-C and phospholipids) in dogs with CTC. Serum leptin correlated positively only with serum  $fT_3$  levels amongst thyroid hormones measured in this study. Similarly, in a previous study<sup>[51]</sup>, circulating thyroid hormones were reported not to play a major role in the regulation of leptin synthesis and secretion. In contrast to previous studies reporting an inverse correlation between serum leptin and cortisol<sup>[39,52]</sup>, in this study, there was no relationship between the two variables in dogs.

The data presented here should be interpreted with caution owing to some limitations. First, a relatively small sample size might not be representative of the dogs with CTC. However, more comprehensive and detailed studies are needed to determine the exact role of leptin and ghrelin, as well as the interactions between them in dogs with CTC.

In conclusion, our study results suggest that serum leptin and ghrelin levels bring up a new perspective which may contribute to clarify pathophysiological mechanisms associated with CTC. Increased serum Hcy and decreased serum folate levels should be taken into consideration at diagnostic and therapeutic approaches in dogs with CTC. Increased serum levels of  $fT_3$  should be interpreted with caution during the diagnostic work-up in dogs suffering from CTC, due to euthyroid sick syndrome.

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