An area ratio of thyroid gland to common carotid artery for evaluating the thyroid gland size

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ABSTRACT. The feasibility of ultrasonographic measurement of thyroid gland area to common carotid artery (TG:CCA) was investigated. Twenty-one healthy, 12 hypothyroid and 18 non-thyroid illness (NTI) dogs were evaluated. The area of thyroid lobe and common carotid artery in right and left sides were measured using the same ultrasonographic images in transverse plane. The average of the right and left ratio was calculated as TG:CCA. The median TG:CCA of 21 healthy dogs was 1.53, and it did not correlate either body weight or age. The median TG:CCA of 12 hypothyroid dogs was 0.81, which was significantly lower than that of 18 NTI dogs (1.81, P<0.001). If the cut off value <1.12 was used, TG:CCA indicated hypothyroidism with a sensitivity of 100%, specificity of 83%, and accuracy of 90%. Our data indicated that TG:CCA was independent of both body weight, which may contribute to consistent measurement of thyroid size. The results of this study suggest that TG:CCA is a promising tool for diagnosing canine hypothyroidism.

KEY WORDS: canine hypothyroidism, non-thyroid illness, thyroid gland, ultrasonography

Hypothyroidism is one of the most common endocrine diseases in dogs. Diagnosis of canine hypothyroidism is still challenging because both nonthyroidal illness (NTI) and concurrently administrated therapeutic agents influence on serological diagnostic tests [5]. Concurrent NTI suppresses the serum thyroid hormone concentrations in euthyroid dogs. Approximately 30% of dogs with NTI had low total thyroxine (T4) concentrations and up to 30% of dogs had low free T4 concentration [7, 8]. Even though the combination of low free T4 and high canine thyroid stimulating hormone (cTSH) concentrations supports the diagnosis of canine hypothyroidism, it sometime is difficult to confirm the diagnosis of primary hypothyroidism in dogs with systemic disorders. Thyroid gland size in canine primary hypothyroidism is decreased due to lymphocytic thyroiditis or idiopathic atrophy [4, 6]. Evaluation of thyroid gland size may be complementary to diagnosis of canine hypothyroidism. Although ultrasound is a minimally invasive imaging modality and has potential to provide high spatial and temporal resolution of thyroid lobe images, it has not fully been investigated that thyroid sonography is useful for diagnosis of canine hypothyroidism. Previous studies showed that ultrasonographic evaluation of thyroid gland size is a promising tool for diagnosing canine hypothyroidism [2, 3, 9]. Those researchers correlated thyroid gland volume to body weight or body surface area, and derived body weight-dependent measures of thyroid gland size. Unfortunately, body weight in individual dogs could change over time because body weight is dependent on the nutritional condition of each dog. In addition, obesity is one of the clinical signs of canine hypothyroidism. A body weight-independent measure of thyroid gland size does not require precise evaluation of body condition or a regression equation, and thus may provide consistent evaluation of thyroid gland size. Here we propose a body weight-independent measure of thyroid gland size, an area ratio of thyroid gland to common carotid artery (TG:CCA) using ultrasonographic images. In this study, we investigated the feasibility of TG:CCA for complementing diagnosis of canine hypothyroidism.
MATERIALS AND METHODS

Animals

Characteristics of TG:CCA were investigated using 21 healthy adult beagles, owned in the laboratory animal facility of the Graduate School of Veterinary Medicine, Hokkaido University. The experiment was approved by the Experimental Animals Committee of the Graduate School of Veterinary Medicine, Hokkaido University (No. 08-0473). None of the dogs had received any medication and had a history of disease or treatment within six months. Results of CBC, serum biochemistry, serum total T4, and endogenous cTSH concentrations were within reference ranges in all dogs.

Twelve hypothyroid and 18 NTI dogs, represented to Hokkaido University Veterinary Teaching Hospital between August 2008 and December 2018, were retrospectively included in assessment of the diagnostic feasibility of TG:CCA. Written informed consent was signed by all owners before the examination. The criteria of hypothyroidism were (1) clinical signs of hypothyroidism, (2) low concentrations of total T4 (<1.5 μg/dl) and free T4 by equilibrium dialysis (<9 pmol/l) with high cTSH concentrations (>0.42 ng/ml), and (3) positive response to thyroxin supplementation. The criteria for NTI were (1) clinical signs of hypothyroidism, (2) low total T4 concentration but normal free T4 by equilibrium dialysis and cTSH were performed at a commercial laboratory (IDEXX Laboratories, Tokyo, Japan). The latest reference level of each hormone at the laboratory was 1.0–4.0 μg/dl, 9.0–47.4 pmol/l, and 0.05–0.42 ng/ml, respectively.

Thyroid sonography

Dogs were positioned in dorsal recumbency without sedation for ultrasound examination, and hairs in small area of larynx were clipped. Thyroid sonography was performed using linear transducers (EUP-L65, Hitachi Medical Corp., Chiba, Japan or PLT-1204BT, Canon Medical Systems, Tochigi, Japan) connected to diagnostic US machines (Hitachi HI VISON Preirus, Hitachi Medical Corp. or Aplio 500, Canon Medical Systems). Thyroid lobes were scanned in transverse and longitudinal plane as previously described [2, 3, 9]. The volume of each thyroid lobe was determined by an ellipsoid formula:

\[ \text{vol (mm}^3) = \frac{\pi}{6} \times \text{length (mm)} \times \text{height (mm)} \times \text{width (mm)} \]

The total thyroid grand volume was calculated as the sum of each thyroid gland volume. The relative thyroid volume was the ratio of the thyroid gland volume to metabolic body weight (kg^{0.75}) [9]. The maximal cross sectional area (MSCA) of thyroid gland was measured and related to metabolic body weights (kg^{0.75}) [9]. The area ratio of thyroid gland to common carotid artery (TG:CCA) was calculated using the transversal image. Both thyroid lobe and common carotid artery (CCA) were observed in the same transversal image, in which thyroid lobe was appeared to be the biggest, with gentle pressure to keep the shape of CCA round (Fig. 1). The thyroid lobe area and the CCA area were measured on the screen of the diagnostic machines using an electronic caliper tool of the machine. The area ratio of each thyroid gland lobe and CCA and TG:CCA were calculated as follows:

\[ \text{area ratio} = \frac{\text{the thyroid lobe area (mm}^2)}{\text{the CCA area (mm}^2)} \]

\[ \text{TG:CCA} = \frac{\text{the right area ratio} + \text{the left area ratio}}{2} \]

To confirm the repeatability and reproducibility of the measurement, TG:CCA was examined 5 times in 5 normal beagles on the same day (intra-observer variability), and 10 times using the same image of one normal beagle (intra-image variability).

Statistical analysis

Statistical analyses were performed with a commercial software (JMP Pro version 14.0, SAS Institute Inc., Cary, NC, USA). The repeatability and reproducibility of the measurement of TG:CCA was evaluated by coefficients of variation (CV).
Correlations between the parameters were determined by Spearman rank correlation test \( (r_s) \). Differences in age and body weight between hypothyroid and NTI dogs were evaluated with Wilcoxon rank sum test. Differences in TG:CCA among healthy beagles, hypothyroid dogs, and NTI dogs was assessed using Steel-Dwass test. A \( P \) value below 0.05 was considered statistically significant. Receiver operating characteristic curve analysis was used to determine an optimal cutoff value for TG:CCA.

**RESULTS**

In 21 normal beagles, the median age was 6 years (range 3–14 years); 12 dogs were intact male and 9 dogs were intact female; and median body weight was 10.7 kg (range 8.1–13.5 kg). The median total thyroid gland volume was 443.6 mm\(^3\) (range 237.3–779.2 mm\(^3\)). Total thyroid gland volume was correlated with body weight \( (r_s=0.59, P=0.005) \) and age \( (r_s=-0.77, P<0.001) \) in 21 beagles (Fig. 2). The median CCA area was 11.5 mm\(^2\) (range 7–18.5 mm\(^2\)), was correlated with body weight \( (r_s=0.45, P=0.04) \) but not age \( (P=0.47) \) in healthy beagles. The median TG:CCA of normal dogs was 1.53 (range 1.00–2.50). While TG:CCA correlated with the total thyroid gland volume \( (r_s=0.45, P=0.04) \), it did not correlate with age \( (P=0.11) \) or body weight \( (P=0.38) \) (Fig. 3). Intra-observer and intra-image CV of TG:CCA were 9.6% and 4.3%, respectively.

Twelve hypothyroid and 18 NTI dogs were included in this study. The disorders of NTI included lethargy and weakness (3), hyperadrenocorticism (2), idiopathic megaesophagus (2), anemia (2), otitis media (1), demodicosis (1), intravertebral disc disease (1), pyoderma (1), idiopathic vestibular disease (1), epilepsy (1), cerebellar infarction (1), malassezia dermatitis (1), meningoencephalitis of unknown origin (1). The median age and body weight of hypothyroid dogs was 10 years (range 6–15 years) and 10.1 kg (range 2.9–32.9 kg), respectively. In hypothyroid dogs, the median serum total T4, fT4, and cTSH concentration was 0.4 \( \mu \)g/dl (range 0.4–0.8 \( \mu \)g/dl), 2.5 pmol/l (range 2.5–5.1 pmol/l), and 1.25 ng/ml (range 0.5–8.61 ng/ml), respectively. The median age and body weight of NTI dogs was 10.5 years (range 3–15 years) and 6.8 kg (range 1.6–31.5 kg), respectively. In NTI

![Fig. 2.](image-url) Relationship between total thyroid gland volume and age (A, \( r_s=-0.77 \)), and between total thyroid gland volume and body weight (B, \( r_s=0.59 \)) in 21 healthy beagles.

![Fig. 3.](image-url) Relationship between thyroid gland area to common carotid artery (TG:CCA) and age (A), and between TG:CCA and body weight (B) in 21 healthy beagles. Neither age nor body weight correlated with TG:CCA.
dogs, the median serum total T4 concentration was 0.9 μg/dl (range 0.6–1.4 μg/dl), and both serum free T4 (median 21.9 pmol/l, range 9–30.9 pmol/l) and cTSH (median 0.14 ng/ml, range 0.06–0.3 ng/ml) concentrations were within the reference range in all dogs. There were no significant differences of age (P=0.72) and body weight (P=0.10) between hypothyroid and NTI dogs. The median TG:CCA of hypothyroid dogs was 0.81 (range 0.43–1.11) and was significantly lower than that of NTI dogs (median 1.81, range 0.92–3.42, P<0.001) (Fig. 4). In 30 clinical cases, TG:CCA correlated with total T4 (r=0.69, P<0.001), free T4 (r=0.74, P<0.001), and cTSH (r=−0.71, P<0.001) concentrations. When the cutoff value for TG:CCA <1.12 was used, the sensitivity for detection of hypothyroidism was 100%, with a specificity of 83% and an accuracy of 90%. The previous study reported the cutoff values were 0.05 (ml/kg0.75) for the relative thyroid gland volume and 3.3 (mm2/kg0.75) for the relative MSCA [9]. If the cutoff value of <0.05 (ml/kg0.75) for the relative thyroid gland volume was used, thyroid sonography in this study indicated hypothyroidism with the sensitivity of 100%, specificity of 50%, and the accuracy of 73%. With the cutoff value for the relative MSCA <3.3 (mm2/kg0.75) was used, the sensitivity was reduced (83%) while the specificity and accuracy were comparable (50% and 73%, respectively).

**DISCUSSION**

The results of this preliminary study shows the feasibility of TG:CCA for evaluating thyroid gland size. TG:CCA was easily obtained with ultrasonography and simple calculation of an area ratio. It must be noted that assessing the diagnostic value of TG:CCA is not the primary object of this study, but that we intend to illustrate this preliminary study that TG:CCA is a body weight-independent measure of thyroid gland size. Previous studies reported that both body weight and age are determinants of thyroid gland volume [2, 9], which was consistent with our study. Interestingly, neither body weight nor age correlated with TG:CCA in the present study. It is likely that the normalization to common carotid artery provides a body weight- and age-independent measurement of thyroid gland size. Normalization to large vessel diameter in the corresponding dimension in echocardiography, i.e. left atrium diameter to aorta ratio [10], is routinely used as a body weight-independent indicator of left atrium dilation. We normalized the thyroid gland size to common carotid artery that was moderately correlated with body weight in this study. Taeymans et al. reported that common carotid size in magnetic resonance imaging was correlated with body weight [12]. The diameter of common carotid artery may correlate better with body frame size than body weight that is dependent on nutritional condition, and thus is less likely to change over time in elder dogs. Our results suggest that TG:CCA may be independent of body weight and be a concise evaluation tool for thyroid gland size.

The measurements of thyroid gland size overlapped between hypothyroid and NTI dogs [3, 9]. Even though the median TG:CCA of hypothyroid dogs was significantly lower than that of NTI dogs, we found a moderate overlap between TG:CCA of two groups. Measurement viability may influence on evaluation of thyroid gland size. An earlier study showed that the highest intra-observer variability was for length due to the shape of lobes and the presence of parathyroid glands [13]. Our method consisted of the area measurement in transverse plane, but not the measurement of the thyroid lobe length. In addition, intra-observer and intra-image CV in this study were comparable to intra-observer CV in the previous study [13]. Inter-observer viability, however, should be investigated in future studies. The relative thyroid gland volume and relative MSCA were useful to discriminate hypothyroidism from NTI because the thyroid measurements had moderate sensitivity and high specificity for canine hypothyroidism [9]. In addition to those two indicators of the thyroid gland size, TG:CCA may be an useful for evaluating the thyroid gland size. Our data suggest that TG:CCA with the high sensitivity may be a potential screening tool for canine hypothyroidism. Unfortunately, the precise diagnostic value of TG:CCA was not fully confirmed because the sample size was not enough to provide both a derivation

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**Fig. 4.** Thyroid gland area to common carotid artery (TG:CCA) of healthy, hypothyroid, and nonthyroidal illness dogs. The median TG:CCA of hypothyroid dogs was significantly lower than that of nonthyroidal illness (NTI) dogs or healthy beagles, there were overlaps among three groups, however. △, healthy beagles (n=21); ●, hypothyroid dogs (n=12); ○, NTI dogs (n=18); bars, median TG:CCA of each group.
and a validation cohort for assessing the cutoff value for TG:CCA. Moreover, the measurement of anti-thyroglobulin autoantibody was not conducted in this retrospective study. It might be possible that some of healthy beagles [1] and NTI dogs had subclinical thyroiditis and progress to hypothyroidism in future. A previous study showed relative thyroid volume decreases during the follow-up of the hypothyroid treatment [11], and the authors suggested that progress of lymphocytic thyroiditis might result in a decrease in thyroid gland size. Future studies may validate an appropriate cut off value for TG:CCA for diagnosing canine hypothyroidism, including subclinical thyroiditis.

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