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Abdominal ultrasonographic findings in acromegalic cats

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Abstract

Objectives Acromegaly is increasingly recognized as a cause of insulin resistance in cats with diabetes mellitus (DM). The objective of this study was to determine if ultrasonographic changes in selected abdominal organs of acromegalic cats could be used to raise the index of suspicion for this condition.

Methods In this retrospective case-control study, medical records of cats presenting to North Carolina State University or Colorado State University from January 2002 to October 2012 were reviewed. Cats were included in the acromegaly group if they had insulin-resistant DM with increased serum insulin-like growth factor (IGF-1) concentrations and had an abdominal ultrasound examination performed with report available. A control group included age-matched cats that had abdominal ultrasound examination performed for investigation of disease unlikely to involve kidneys, adrenal glands, pancreas or liver.

Results Twenty-four cats were included in each group. IGF-1 concentrations in the acromegaly group ranged from >148 to 638 nmol/l. When compared with age-matched controls, cats with acromegaly demonstrated significantly increased median left and right kidney length, significantly increased median left and right adrenal gland thickness, and significantly increased median pancreatic thickness. Hepatomegaly and bilateral adrenomegaly were reported in 63% and 53% of acromegalic cats, respectively, and in none of the controls. Pancreatic abnormalities were described in 88% of the acromegalic cats and 8% of the controls.

Conclusions and relevance These findings indicate that compared with non-acromegalic cats, age-matched acromegalic patients have measurably larger kidneys, adrenal glands and pancreas. Diagnostic testing for acromegaly should be considered in poorly regulated diabetic cats exhibiting organomegaly on abdominal ultrasound examination.

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Introduction

Hypersomatotropism with associated acromegaly is increasingly recognized as a cause of insulin resistance in feline diabetic patients.[1–4] Acromegaly is the clinical syndrome that results from excessive secretion of growth hormone (GH) from a functional somatotropic adenoma of the pars distalis of the pituitary gland.[5] The clinical signs of the disease have classically been attributed to the catabolic effects of GH, the anabolic effects of insulin-like growth factor-1 (IGF-1) and the space-occupying effect of the pituitary adenoma.[3,5,6] GH exerts its catabolic effects through a postreceptor defect in the action of insulin on target cells, leading to decreased carbohydrate utilization, reduced insulin sensitivity and hyperglycemia.[5,7] GH also stimulates the production of IGF-1, primarily by the liver, resulting in increased protein synthesis and excessive tissue growth.[8] The diagnosis of feline acromegaly currently relies on demonstrating the

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combination of insulin-resistant diabetes mellitus (DM), typical physical changes and increased serum IGF-1 concentrations.[4] Owing to limited assay availability, GH measurement is not widely used to make the diagnosis. Further confirmation can be provided by demonstration of a pituitary tumor with computed tomography (CT) or magnetic resonance imaging (MRI).[9,10]

Acromegaly is one of multiple causes of insulin resistance in diabetic cats, a clinical problem for which the diagnostic work-up can be extensive.[2] Commonly reported physical characteristics of the disease in cats include weight gain, prominent facial features, arthropathy, respiratory stridor and organomegaly.[2,4,11] Recent studies have documented skull and soft tissue changes in the heads of acromegalic cats examined by MRI and CT,[12,13] and ultrasonographic changes in abdominal organs have been alluded to in other studies and reviews of the disease.[5,10,14] The aim of this study was to quantitate the ultrasonographic changes in the abdominal organs of acromegalic cats, with the purpose of identifying features that could suggest a diagnosis of acromegaly and support the early measurement of IGF-1 in diabetic cats with insulin resistance. The hypothesis was that compared with non-acromegalic cats, acromegalic cats would demonstrate on abdominal ultrasound examination enlargement of the kidneys, adrenal glands, pancreas and liver.

Materials and methods

Study population

Medical records at the veterinary teaching hospitals at North Carolina State University (NCSU) and Colorado State University (CSU) were searched to identify cats with poorly regulated DM that had serum IGF-1 measured and received an abdominal ultrasound examination between January 2002 and October 2012. DM was determined to be poorly regulated if the insulin dose was ⩾5 IU/injection or ⩾1 IU/kg/injection, with persistent hyperglycemia and unresolved clinical signs of DM. Cats were included in the acromegaly group if they had serum IGF-1 concentrations more than twice the upper limit of the reference range, a normal serum total thyroxine documented within 6 months of the abdominal ultrasound examination and an ultrasound report available. Cats were excluded from the acromegaly group if the abdominal ultrasound examination was performed prior to the onset of insulin resistance and if any other cause of insulin resistance was identified. Following identification of the acromegaly group, an equal number of control cats were identified by searching the medical records at NCSU for cats within the age range of the acromegaly group that had abdominal ultrasound examination performed with a report available. Inclusion criteria included documentation of presenting complaint, complete history, physical examination, complete blood count (CBC) and serum biochemistry profile within 14 days of the abdominal ultrasound examination. Cats were excluded from the control group if they had any historical, clinical or clinicopathological evidence of DM or of disease likely to involve the kidneys, adrenal glands, pancreas and liver, and if intra-abdominal neoplasia was detected on abdominal ultrasound examination.

Data collected

For the acromegaly and control groups, age, breed, sex and body weight (kg) were recorded. For the acromegaly group, insulin type and dose, serum IGF-1 concentration and results of brain imaging, if performed, were recorded. For the control group, the reason for performing abdominal ultrasound examination was documented. For both groups, left and right renal length, left and right adrenal gland thickness, and thickness of the left limb of the pancreas were recorded (mm). Values were obtained from the ultrasound report or from measurements recorded on saved images if measurements were not separately documented in the ultrasound report. Adrenal thickness was recorded as the greatest diameter measured perpendicular to the long axis of the adrenal gland. The left limb of the pancreas was assessed as this region of the pancreas was most consistently imaged and measured in the cats. Subjective comments regarding the appearance of the pancreas and liver were also recorded when present in the ultrasound report. The convention at CSU and NCSU is that if specific comments are not recorded on the ultrasound report for an organ, that organ is regarded as normal in appearance. All ultrasound examinations were performed or directly supervised by board-certified veterinary radiologists.

Statistical analysis

Length of the left and right kidneys, thickness of the left and right adrenal glands and thickness of the left limb of the pancreas were compared between the acromegaly and control group with a one-tailed Mann–Whitney test. Proportions of changes noted in the two groups were compared with Fisher's exact test. All analyses were performed using commercially available software (Prism; GraphPad Software). A P value <0.05 was considered to be statistically significant.

Results

Study population

Eleven cats evaluated at NCSU and 13 cats evaluated at CSU met the criteria for inclusion in the acromegaly group (n = 24). Twenty-four non-diabetic feline patients with abdominal ultrasound examination performed at NCSU were included in the control group. Based on the presenting complaint, history, physical examination findings, and evaluation of the CBC and serum

biochemistry profile, none of these cats were suspected to have renal, hepatic or pancreatic disease prior to abdominal ultrasound examination. The reasons for performing abdominal ultrasound examination in this group included staging for extra-abdominal neoplasia or suspected neoplasia (sarcoma: n = 4; nasal mass: n = 3; solitary lymph node lymphoma: n = 2; mammary adenocarcinoma: n = 1; lung mass: n = 1; mediastinal mass: n = 1; oral squamous cell carcinoma: n = 1; spinal cord mass: n = 1; axillary mass: n = 1), lower urinary tract signs (n = 3), non-cardiogenic pleural effusion (n = 2), epistaxis (n = 2), anterior lens luxation (n = 1), and uveitis (n = 1). The signalment and weight of the acromegaly and control groups are summarized in Table 1.

Acromegaly group: insulin therapy

Seventeen of the 24 acromegalic cats were managed with glargine insulin, four with protamine zinc insulin, one-with detemir, one with ultralente insulin and one with lente insulin. The mean and median total insulin doses were 12 and 10 IU per dose, respectively (range 4–42 IU). The mean and median dose/kg were 2.1 IU/kg and 1.7 IU/kg, respectively (range 0.8–8.1 IU/kg).

Acromegaly group: serum IGF-1 concentration

Serum IGF-1 concentration ranged from >148 nmol/l to 638 nmol/l. The value of >148 nmol/l was recorded in 2003 when the reference range for the laboratory was 5–70 nmol/l. For all other cats, the reference range was 12–92 nmol/l. Mean and median serum IGF-1 concentrations for the acromegaly group were 376 and 367 nmol/l, respectively. In all cases the serum IGF-1 assay was performed at the Diagnostic Center for Animal and Population Health at Michigan State University, using a commercially available radioimmunoassay.

Acromegaly group: brain imaging

Brain imaging was performed in 14 of the cats with acromegaly. Ten cats underwent CT alone, one had MRI alone, and three cats underwent both CT and MRI examination. A pituitary mass or enlarged pituitary gland was detected in 13 cats.

Abdominal ultrasound examination findings: measurements

Renal length was documented for both kidneys in all 24 of the control cats and in 22 of the cats in the acromegaly group; in the remaining two cats, length was recorded as 'normal', but measurements were not available. Median left and right kidney lengths were 47 mm (range 35–62 mm) and 47 mm (range 35–61 mm), respectively, in the acromegaly group. Median left and right kidney lengths were 39 mm (range 30–47 mm) and 42 mm (range 26–51 mm), respectively, in the control group. Median left and right kidney lengths were significantly greater in the acromegaly group compared with controls (left: $P < 0.0001$; right: $P = 0.0005$). These results are illustrated in Figure 1. When compared with a published normal range of renal length in cats of 30–43 mm,[15] left renomegaly was present in 18/22 (82%) acromegalic cats, and right renomegaly was present in 18/22 (82%) cats. Renal length exceeded the published normal range in both kidneys in 16/22 (73%) acromegalic cats in which measurements were available. In the control cats, kidney length exceeded the normal range in 5/24 (21%) left kidneys and in 9/24 (38%) right kidneys, with 5/24 (21%) cats demonstrating bilateral renomegaly. Significantly more cats in the acromegaly group demonstrated bilateral renomegaly ($P < 0.0009$).

Table 1 Signalment and weight of acromegaly and control cats

		Acromegaly (n = 24)	Control (n = 24)
Age (years)	Mean	11.1	10.2
	Median	11.5	10
	Range	7–15	7–13
Breed	Domestic shorthair	18	18
	Domestic longhair	5	3
	Siamese	1	3
Sex	Castrated male	19	15
	Spayed female	5	9
Weight (kg)	Mean	5.85	5.90
	Median	5.60	5.42
	Range	4.14–9.02	2.71–11.70

The results of the adrenal gland measurements are shown in Figure 2. Median left and right adrenal gland

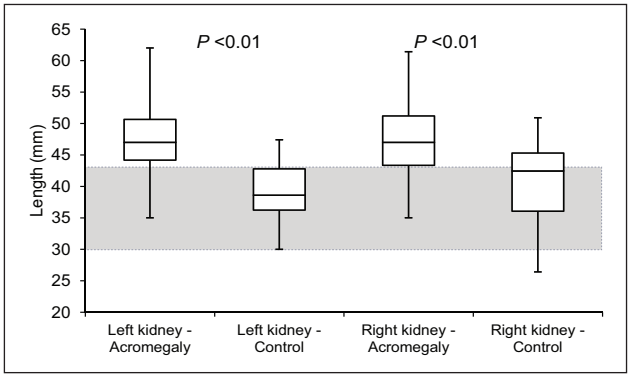

Figure 1 Renal length in acromegalic cats (n = 22) compared with control cats (n = 24). Results are shown as box and whisker diagrams. The central box represents the values from the lower to upper quartile. The middle line represents the median. The vertical line extends from the minimum to the maximum value. The gray area indicates the reference range.[15] The *P* value reflects the comparison between normal and acromegaly. A *P* value <0.05 was considered to be statistically significant

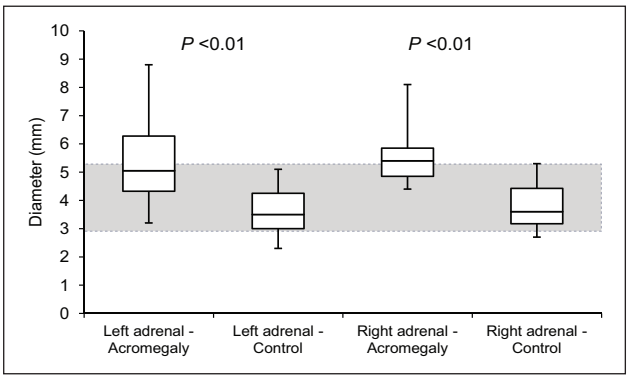

Figure 2 Adrenal thickness in acromegalic cats (n = 16 for the left adrenal; n = 13 for the right adrenal) compared with control cats (n = 24 for the left adrenal; n = 22 for the right adrenal). Results are shown as box and whisker diagrams as described for Figure 1. The gray area indicates a combined reference range for normal left and right adrenal glands[16]

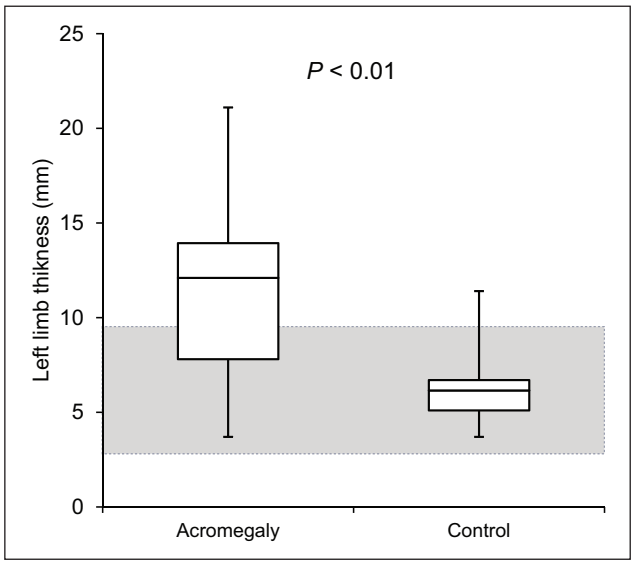

Figure 3 Thickness of the left limb of the pancreas in acromegalic cats (n = 10) compared with control cats (n = 19). Results are shown as box and whisker diagrams as described for Figure 1. The gray area represents the reference range[16]

thicknesses were 5.1 mm (range 3.2–8.8 mm; n = 16) and 5.4 mm (range 4.4–8.1 mm; n = 13), respectively, in the acromegaly group. Median left and right adrenal gland thicknesses were 3.5 mm (range 2.3–5.1 mm; n = 24) and 3.6 mm (range 2.7–5.3 mm; n = 22), respectively, in the control group. Median adrenal gland thickness was significantly greater in the acromegaly group compared with controls (left: $P < 0.0001$; right: $P < 0.0001$). Compared with the normal range of healthy feline adrenal thicknesses of 3.0–5.3 mm for the left and 2.9–4.5 mm for the right,[16] bilateral adrenomegaly was present in 7/13 acromegalic cats (54%) that had both adrenal glands measured. Left adrenomegaly was present in 7/16 (44%) acromegalic cats for which measurements were available, and right adrenomegaly was present in 11/13 (85%) acromegalic cats for which measurements were available. In the control group, thickness of the right adrenal gland was greater than the published normal range in 4/22 (18%) cats for which measurements were available. None of the measured left adrenal glands exceeded the normal range for thickness in the control cats. Significantly more cats in the acromegaly group demonstrated bilateral adrenomegaly ($P = 0.0003$).

Thickness of the left limb of the pancreas was documented for 10 cats in the acromegaly group and 19 cats in the control group, with medians of 12.1 mm (range 3.7–21.1 mm) and 6.1 mm (range 3.7–11.4 mm), respectively. The left limb of the pancreas was significantly thicker in the acromegalic cats compared with the controls ($P = 0.001$). These results are shown in Figure 3. Thickness of the left limb of the pancreas was increased above a published reference range (2.6–9.5 mm)[17] in 6/10 (60%) cats in the acromegaly group and 1/19 (5%) cats in the control group. Significantly more cats in the acromegaly group demonstrated increased thickness of the left limb of the pancreas ($P = 0.0026$).

Abdominal ultrasound examination findings: descriptive changes

Comments regarding the ultrasonographic appearance of the pancreas were documented in 16 of the 24 cats in the acromegaly group. The pancreas was noted to be hypoechoic in 12 cats, thickened or enlarged in nine cats, containing nodules in five cats and containing cysts in two cats. The pancreas was noted to be ultrasonographically normal in two cats in the acromegaly group. In the control group, no comments were noted regarding the pancreas in 22/24 cats. One cat was noted to have a few small nodules in the pancreas, and one cat had several nodules and cysts within the pancreas. The latter cat was also the only cat in the control group for which the thickness of the left limb of the pancreas was demonstrated to be above the reference range. Significantly more cats in the acromegaly group were noted to have pancreatic abnormalities on abdominal ultrasound examination ($P < 0.0001$).

The liver was described as subjectively enlarged in 15/24 cats (63%) in the acromegaly group and in none of the cats in the control group. The liver was noted to be hyperechoic in 17/24 cats, hypoechoic in three cats, of normal echotexture in three cats, of mixed echogenicity in one cat, to contain nodules in seven cats and to contain cysts in two cats in the acromegaly group. In the control group, liver abnormalities were noted in a total of five cats. Two cats were noted to have a mildly hyperechoic liver, one cat had a suspected biliary cystadenoma, one cat had a single focus of

mineralization, and one cat had non-specific hypoechoic nodules in the liver. Cats in the acromegaly group were significantly more likely to have hepatomegaly ($P < 0.0001$) and significantly more likely to have hepatic abnormalities or changes in echogenicity noted on the ultrasound report ($P < 0.0001$).

Discussion

The results of this study confirm that acromegalic cats, when compared with non-acromegalic cats, have measurably enlarged kidneys, adrenal glands and pancreas, and a subjectively enlarged liver, as assessed by abdominal ultrasound examination.

Difficulty in achieving optimal glycemic control in feline diabetic patients is a clinical problem for which the list of differential diagnoses is extensive. A thorough investigation is needed for evaluation of poorly regulated DM, and abdominal ultrasound studies are commonly carried out for this purpose. Hypersomatotropism causes organomegaly through the anabolic effects of IGF-1, and while the development of organomegaly is widely accepted and well described as a feature of acromegalic patients on physical examination and necropsy,[4,8] no peer-reviewed studies to date have described the ultrasonographic characteristics of the abdominal organs of acromegalic cats in comparison with control cats. The finding that abdominal organomegaly is detected on ultrasound examination of cats with acromegaly is important, as it may serve to increase suspicion of acromegaly and support early testing for this disease through measurement of serum IGF-1 concentrations.

Insulin resistance is defined as decreased sensitivity to insulin, and although there is no specific insulin dose that is diagnostic for insulin resistance, most diabetic cats can be controlled on insulin doses ranging from 1–3 IU per dose, or <1 IU/kg.[18] All cats included in the acromegaly group were referred for poorly regulated DM and were receiving an insulin dose of at least either 5 IU per dose or 1 IU/kg per dose, with no other identified cause of insulin resistance. The diagnosis of acromegaly was based on detection of a significantly increased serum IGF-1 concentration, and cats were only included in the acromegaly group if the serum IGF-1 concentration was at least twice the upper limit of the reference range. This high cut-off value was used to increase the specificity of the test, as it has previously been shown that poorly regulated diabetic cats may have modestly increased serum IGF-1 levels.[4]

The age, breed and sex of the acromegalic cats included in this study were comparable with the published literature that describes the typical acromegalic population as middle-aged to older neutered male domestic shorthair cats.[3,5,8,19] Because acromegaly more commonly affects older cats, an age-matched control group was included for comparison in order to overcome any possible effects of aging on the ultrasonographic appearance and size of the organs of interest. A positive correlation between renal length and body weight has been reported in both cats and dogs.[20,21] Differences in renal length among feline breeds have also been described.[22] However, in addition to being of a comparable age, the cats included in the acromegaly and control groups had similar body weight and breed distribution. There was a greater proportion of spayed female cats in the control group compared with the acromegaly group; however, it has been shown that there is no significant difference in renal length between neutered male and spayed female cats on abdominal radiographs.[23] A number of abdominal ultrasound studies have evaluated adrenal gland size in healthy and sick cats, and have demonstrated no difference in adrenal gland size between male and female cats, between cats of different breeds, or between healthy and chronically sick cats.[16,24] Hepatic size is difficult to evaluate objectively on abdominal ultrasound examination[25] however, hepatomegaly was noted subjectively in approximately two-thirds of the acromegalic cats and in none of the control cats. Acromegalic cats were more likely than control cats to have an enlarged pancreas with changes such as diffuse hypoechogenicity or the presence of nodules.

There are several limitations to this retrospective study. First, several different ultrasonographers performed the ultrasound studies, potentially causing inconsistencies in the descriptive data. While having different ultrasonographers introduces variability in subjective data, it is also more representative of clinical reality. Secondly, the ultrasonographers were not blinded to the clinical presentations of the cats, which is a potential source of bias. This is particularly relevant for the acromegaly group, as these cats were presented for insulin resistance and therefore the ultrasonographer might be expected to more critically evaluate the appearance of the abdominal organs, particularly the adrenal glands and pancreas. However, this bias is of less concern when comparing objective measurements of organ size. A further limitation of this retrospective study is that it was not possible to determine the duration of the signs of acromegaly from the available medical records; thus, it is not known if the findings can be applied to cats that are evaluated early in the disease process. Finally, it could be argued that the diagnosis was not definitive in all the cats in the acromegaly group. All cats in this group had markedly increased serum IGF-1 levels with concurrent DM with insulin resistance; however, GH was not measured owing to limited availability of the assay. A pituitary mass or enlarged pituitary gland was documented in 13/14 cats that underwent advanced brain imaging. When the abdominal ultrasound findings from these 13 cats were analyzed separately (data not shown), renal length, adrenal gland thickness and thickness of the left limb of the pancreas were all significantly increased in the acromegaly group with pituitary abnormalities compared with controls.

The selection of a control group was challenging in this retrospective study. Clinically normal cats in the age range of the acromegaly group could be used as controls, but these patients rarely undergo abdominal ultrasound examination. Conversely, sick cats in this age range are often evaluated for suspected disease of the organs targeted in this study. Thus, we selected cats that underwent abdominal ultrasound examination with no suspicion of disease involving the kidneys, adrenal glands, pancreas or liver. A control group of cats with DM without acromegaly was considered desirable, but unfortunately it was not possible to identify a sufficient number of diabetic cats with documented normal serum IGF-1 concentrations and no evidence of renal, adrenal, pancreatic or hepatic disease. However, it should be noted that a 2007 ultrasound study demonstrated that the adrenal glands of diabetic cats were not enlarged when compared with those of healthy cats, suggesting that the adrenal gland enlargement detected in the present study is associated with acromegaly, and not due to DM itself.[26]

Conclusions

Acromegalic cats have measurably enlarged kidneys, adrenal glands and pancreas, and a subjectively enlarged liver, when compared with age-matched non-acromegalic cats evaluated ultra sonographically. Measurement of serum IGF-1 concentrations should be considered in insulin-resistant diabetic cats that are found to have enlargement of these organs on abdominal ultrasound examination.

Conflict of interest The authors have no potential conflicts of interest to declare.

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