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Adrenocorticotrophic hormone causes an increase in cortisol, but not parathyroid hormone, in dogs



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ABSTRACT

Dogs with spontaneous disorders of glucocorticoid production often have marked disturbances in calcium homeostasis. For example, hypercalcaemia is frequently observed in dogs with hypoadrenocorticism and secondary hyperparathyroidism is a common feature of canine hyperadrenocorticism. The mechanism(s) by which glucocorticoids modulate calcium homeostasis in dogs remains ill-defined. The hypothesis of this study is that a marked increase in serum cortisol concentrations would lead to an immediate negative calcium balance state which would drive a compensatory increase in parathyroid hormone (PTH) concentrations. This hypothesis was investigated by measuring serum cortisol and plasma PTH concentration in 19 dogs before and after administration of adrenocorticotrophic (ACTH) hormone. Post ACTH administration, there was a significant increase in serum cortisol, but not PTH, concentrations. The results of this study do not support the hypothesis that an increase in endogenous glucocorticoids influences calcium balance sufficiently to cause an immediate, compensatory increase in parathyroid hormone concentration.

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Dogs with spontaneous disorders of glucocorticoid production often have markedly disturbed calcium homeostasis. For example, approximately 30% of dogs with primary hypoadrenocorticism, a condition in which dogs have deficient production and secretion of glucocorticoids, present with hypercalcaemia (Adamantos and Boag, 2008; Peterson et al., 1996). Despite hypercalcaemia being a feature of hypoadrenocorticism, the pathogenesis of this complication remains poorly understood. A recent study of calcium homeostasis in hypercalcaemic dogs with hypoadrenocorticism found that the concentrations of parathyroid hormone (PTH), parathyroid hormone related protein (PTHrp) and 1,25 dihydroxyvitamin D (1,25(OH)₂D), which can all increase serum calcium concentrations, were within their respective reference ranges (Gow et al., 2009). A range of other explanations have been proposed to explain the development of hypercalcaemia in the absence of glucocorticoids including decreased glomerular filtration of calcium and/or increased tubular calcium reabsorption, excessive intestinal absorption of calcium and

increased bone resorption (Hahn et al., 1981; Rath and Reddi, 1979; Walker and Davies, 1981; Walser et al., 1963).

Conversely, dogs with hyperadrenocorticism, where either an ACTH production pituitary tumour or an adrenal tumour results in the excessive production of glucocorticoids, frequently have increased plasma concentrations of PTH (Ramsey et al., 2005). Again, the pathophysiology of this condition is poorly understood although a negative calcium balance, direct stimulation of PTH secretion by cortisol, altered vitamin D metabolism and increased phosphate balance have been postulated to be important (Ramsey et al., 2005).

A plausible explanation for the alterations in calcium homeostasis which occur in glucocorticoid disorders in dogs is that an absence of glucocorticoids leads to an increased calcium balance whereas an excess leads to a reduced calcium balance through altered gastrointestinal and/or renal handling of calcium. This hypothesis would lead to the prediction that dogs with an excess of glucocorticoids would have a reduced calcium balance which would cause PTH concentrations to increase in order to maintain calcium within the reference range whereas an absence of glucocorticoids would cause an increased calcium balance resulting in a PTH concentration within or below the reference range. This hypothesis is compatible with the clinical observations that PTH concentrations are frequently increased in dogs with hyperadrenocorticism and are within or below the reference range in dogs with hypoadrenocorticism (Gow et al., 2009; Ramsey et al., 2005).

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In order to examine this hypothesis further, we measured PTH concentrations before and after an ACTH stimulation test in dogs undergoing adrenal function testing assessed as part of their standard clinical assessment, where we were interested in assessing adrenal function further. Administration of ACTH typically results in a significant increase in cortisol in dogs with normal adrenal function (Cohen and Feldman, 2012). We predicted that PTH, which has a short half-life and can rapidly increase in response to physical exertion and quickly decreases follow parathyroidectomy (Graham et al., 2012; Tsai et al., 1997), would increase in response to the increased serum concentrations of cortisol.

Consecutive cases of dogs which were undergoing an ACTH stimulation test as part of their standard clinical evaluation were considered eligible for inclusion in the study. A serum and EDTA plasma sample was collected prior to the intravenous administration of 0.125 mg i.v. of tetracosactide acetate (Nycomed Austria GmbH, St-Peter-Strasse 25, A-4020 Linz, Austria) (dogs up to 5 kg) or 0.25 mg i.v. of tetracosactide acetate (dogs >5 kg). Serum cortisol was measured immediately and 1 hour post the intravenous administration of tetracosactide acetate by immulite immunoassay (Siemens Medical Solutions Diagnostics, Healthcare Sector, Henkestrasse 127, D-91052 Erlangen, Germany) (reference range 20–230 nmol/l). Serum total calcium was measured using a Ilab650 biochemistry analyser, Diamond Diagnostics, USA. Samples for parathyroid hormone measurement were collected by immediately separating and freezing plasma from blood collected into EDTA tubes. The samples were stored at -70°C before sending to laboratory for analysis on dry ice. The plasma PTH concentrations were measured using a canine intact PTH ELISA (Immutopics International, 931 Calle Negocio, Suite G, San Clemente, California, USA). Pre- and post-ACTH cortisol and PTH concentrations were compared using a paired Wilcoxon test. Significance was set at $p < 0.05$. The study was approved by the University of Edinburgh Veterinary Ethics Research Committee.

Nineteen dogs were included in the study. Fourteen breeds of dog were represented. There were 3 neutered males, 5 intact males and 10 neutered females. The median age of the dogs was 102 months (range 25–157 months). Ten dogs had a final diagnosis of inflammatory bowel disease. One was diagnosed with hyperadrenocorticism, 4 with chronic hepatitis, 2 with pyelonephritis, 1 with diabetes insipidus and 1 with chronic renal disease. Sixteen dogs had serum calcium values within reference range (2.3–3 mmol/l) with a medium calcium value of 2.4 mmol/l and a range of 1.74 mmol/l–2.96 mmol/l. Two dogs had mild hypocalcaemia. Serum cortisol concentrations increased following ACTH administration ($p < 0.0001$, Fig. 1, median pre 80.3 nmol/l, median post 459.5 nmol/l). The mean plasma PTH concentrations did not increase following

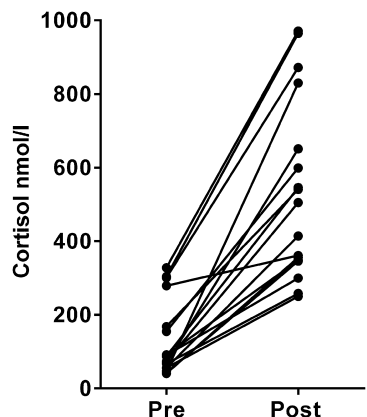


Fig. 1. Serum cortisol concentrations pre and post ACTH administration.

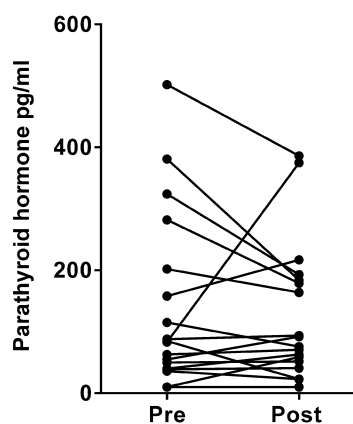


Fig. 2. Plasma parathyroid hormone concentrations pre and post ACTH administration.

ACTH administration ($p = 0.48$, Fig. 2, median pre 84 pg/ml, median post 84 pg/ml; range pre <10.0 pg/ml–502 pg/ml and range post <10.0 pg/ml–530 pg/ml) (reference range 20–65 pg/ml).

The central finding of this study is that ACTH significantly increases cortisol in dogs but has no impact on short term PTH concentrations. This observation is consistent with our previous work that found that PTH concentrations did not increase in dogs with atopic dermatitis following a 7 week course of a therapeutically effective dose of prednisolone (Kovalik et al., 2012). Together, these findings argue against the hypothesis that glucocorticoids cause a negative calcium balance in dogs since a significant increase in renal loss of calcium or a decrease in intestinal absorption of calcium would trigger an increase in PTH concentrations. However, our current study, which only longitudinally tracked PTH concentrations for 1 hour post ACTH administration, does not exclude the possibility that PTH concentrations may increase at later timepoints. The findings in this study are also consistent with studies in humans which found that PTH concentrations did not increase following glucocorticoid therapy (Hahn et al., 1981; Prummel et al., 1991; Seeman et al., 1980).

The lack of increase in PTH in response to a short term increase in cortisol or to a therapeutically effective dose of prednisolone contrasts with the finding that PTH is typically increased in dogs with hyperadrenocorticism (Ramsey et al., 2005). The reason(s) for this difference are unclear but may relate to a greater magnitude and duration of glucocorticoid excess which typically occurs in dogs with hyperadrenocorticism.

The findings of this study also contrast with reports in humans administered ACTH for infantile spasms, which has been associated with nephrocalcinosis and osteoporosis side effects (Katzir et al., 1992; Riikonen et al., 1986). Chronic administration of ACTH can result in hypocalcaemia, an increase in urinary excretion of calcium and an increase in serum parathyroid hormone (Riikonen et al., 1986). The differences between our study and the findings in humans may relate to the dose and duration of ACTH administration. The failure of an increase in glucocorticoids to cause an immediate increase in plasma PTH concentration in dogs also differs from the ex-vivo observation that cortisol can increase PTH secretion from parathyroid tissue (Au, 1976). However, the measurement of PTH on one occasion post ACTH administration may fail to detect glucocorticoid induced alterations in the pulsatile secretion dynamics of PTH which have been reported to occur in short term treatment with glucocorticoids (Bonadonna et al., 2005).

The findings of this study and our earlier work do not support the concept that glucocorticoids modulate calcium balance in dogs. Additional studies examining PTH concentrations at several timepoints post ACTH administration would be informative since

PTH concentrations may increase at later timepoints. Studies examining urinary fractional excretion of calcium in dogs with either hypoadrenocorticism or hyperadrenocorticism pre- and post-treatment would be helpful in further examining whether glucocorticoids induce a negative calcium balance in dogs with spontaneous disorders of glucocorticoid metabolism. All dogs in this study had an underlying disease and underwent an ACTH stimulation as part of their standard diagnostic evaluation. Consequently, the findings in this study cannot be directly extrapolated to healthy dogs. Finally, additional studies examining whether glucocorticoids modulate gastrointestinal absorption of calcium would be valuable.

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