Plasma insulin-like growth factor-1 concentration in dogs with chronic enteropathies

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ABSTRACT: Plasma concentrations of insulin-like growth factor (IGF)-1 were examined in dogs suffering from food-responsive diarrhea (group FRD) or inflammatory bowel disease (group IBD) before and after treatment and compared with IGF-1 values in healthy dogs (group C). Blood of 76 dogs was sampled (FRD before treatment, n = 23; IBD before treatment, n = 11; C, n = 42) and after treatment (FRD, n = 15; IBD, n= 8) with a hypoallergenic diet combined with (group IBD) or without prednisolone (group FRD). A clinical score (Canine IBD Activity Index = CIBDAI) was applied to judge the health status in all dogs. Plasma concentration of IGF-1, of total protein, albumin, glucose, urea, non-esterified fatty acids (NEFA), and of the acute phase protein haptoglobin was measured in all dogs. The CIBDAI scores decreased during the treatment period in FRD and IBD ($P < 0.05$). IGF-1 concentrations were positively correlated with body weight (BW) ($r_{sp} = 0.65$, $P < 0.001$) and values of IGF-1 were therefore normalized with BW. IGF-1/BW ratios were lower in FRD and IBD before treatment than in C ($P < 0.01$). IGF-1/BW ratios increased in FRD ($P < 0.05$) dogs during treatment. Plasma glucose concentration was lower in FRD dogs before treatment than in C ($P < 0.05$), and NEFA concentrations were higher in FRD dogs before and after treatment than in C ($P < 0.001$). Haptoglobin concentrations were higher in IBD dogs before and after treatment than in all other groups ($P < 0.05$). In conclusion, chronic enteropathies reduce the plasma IGF-1 status in dogs. The increase of the IGF-1/BW ratio after treatment suggests that plasma IGF-1 concentration may help to judge the outcome of chronic enteropathies in dogs.

Keywords: plasma insulin-like growth factor; metabolites; haptoglobin; food responsive diarrhea; inflammatory bowel disease

Catabolism and growth impairment are known complications of chronic inflammations and are associated with changes in the somatotropic axis (Elsasser et al., 1997, 2000). This may also be the case during inflammatory bowel disease (IBD) of dogs. Studies in human IBD patients revealed reduced serum levels of insulin-like growth factor (IGF)-1 and IGF-binding-protein (IGFBP)-3 compared to healthy individuals (Beattie et al., 1998; Katsanos et al., 2001). Plasma IGFBP-3 concentration increased during remission in parallel with IGF-1 levels (Baxter, 2001; Corkins et al., 2003). After treatment with high doses prednisolone, plasma IGFBP-3 was at the same level as in con-

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trols, and plasma total IGF-1 moved towards levels measured in controls (Gronbaek et al., 2002).

Chronic enteropathies (CE) are a frequent problem of dogs presented at veterinary clinics (Allenspach and Gaschen, 2003). Food responsive diarrhea (FRD) and idiopathic IBD are the main differential diagnoses for chronic diarrhea. These intestinal disorders are chronic in nature and the majority of cases have frequent relapses of clinical disease throughout life. The impaired health status in these dogs as indicated by increased Canine Inflammatory Bowel Disease Activity Index (CIBDAI) probably also expresses systemic metabolic and endocrine effects beyond the GIT (Jergens et al., 2003).

There is little published information on the IGF-1 status in dogs. Eigenmann et al. (1984a,b), Maxwell et al. (1998a) and White et al. (1999) showed that IGF-1 plasma concentration in dogs correlate well with body weight (BW) and might be used as an indicator for growth potential. Furthermore, Blum et al. (1992) showed that differences in energy intake influence plasma IGF-1 levels in growing dogs. IGF-1 reflects the nutritional status (Zentek et al., 2003). However, to the best of our knowledge, published information on plasma IGF-1 in dogs with CE is lacking.

Based on these premises we tested the hypothesis that repeated measurements of IGF-1 plasma concentrations can help to judge disease development in canine FRD and IBD. The goal of this study was to establish baseline values of IGF-1 plasma concentrations in a mixed population of adult dogs and to investigate the influence of disease, BW, sex, and age on plasma IGF-1 concentrations.

MATERIAL AND METHODS

Animals

All experimental procedures were approved by the Committee overseeing Animal Experimentation in Bern (Number 72/02) and by the Ethical Committee of the Vetsuisse Faculty, University of Bern.

Thirty-four privately owned dogs were referred by their veterinarians to the Small Animal Teaching Hospital, University of Bern, for diagnostic gastro-, duodeno- and colonoscopy in the frame of a large study on chronic enteropathies in dogs. Recruitment criteria have been described elsewhere (Allenspach et al., 2004; Sauter et al., 2005b). A clinical score was applied to judge the severity of disease. Scoring criteria of CIBDAI include attitude, activity, appetite, vomiting, stool consistency, stool frequency, and weight loss (Jergens et al., 2003). The total CIBDAI score determines the clinical severity of disease as follows: 0–3 = healthy or clinically insignificant gastrointestinal symptoms; 4–5 = mild gastrointestinal symptoms; 6–8 = moderate gastrointestinal symptoms; ≥9 = severe gastrointestinal symptoms.

Dogs were retrospectively classified as FRD or IBD based on clinical, endoscopical, histopathological findings and on responsiveness to an elimination diet [Purina Canine LA® (Limited Antigen) Diet, St. Lous, MO]. Dogs classified as IBD needed additional treatment with prednisolone [1 mg/kg body weight (BW) twice daily for 10 days, then 0.5 mg/kg twice daily for 10 days, then 0.5 mg/kg once daily for 10 days, then 0.5 mg/kg every other day for 10 days].

Twenty-three dogs were classified as FRD before treatment (FRD^{bef}) [8 females, 15 males, mean age 29 months (range 7 to 77 months), mean BW 29 kg (range 2 to 56 kg), mean duration of symptoms 10 ± 2 months]. Fifteen dogs [6 females, 9 males, mean BW 31 kg (range 8 to 56 kg)] were presented for a second examination after 4 weeks of treatment (FRD^{aft}). Eight dogs did not come back for a second examination and sampling either because they needed additional treatment due to other diseases or because of owner's incompliance. Eleven dogs were classified as IBD before treatment (IBD^{bef}) [4 females, 7 males, mean age 77 months (range 6 to 139 months), mean BW 25 kg (range 4 to 71 kg), and mean duration of symptoms 17 ± 3 months]. Eight dogs [4 females, 4 males, mean BW 25 kg (range 4 to 71 kg)] were presented for second examination and sampling (IBD^{aft}). Two dogs did not come back for the second examination due to owner's incompliance. One dog had to be euthanized because his health status rapidly deteriorated.

The control group (C) consisted of 42 gastro-intestinally healthy dogs [18 females, 24 males, mean age 53 months (range 4 to 168 months), mean BW 27 kg (range 5 to 72 kg)]. They had no clinical evidence of disease and physical and laboratory examinations were unremarkable. Dogs were either healthy blood donors at the small animal clinic of the University of Bern or belonged to a Swiss Army station in Bern.

Table 1 summarizes the breeds represented in group FRD, IBD and C dogs.

Table 1. Breed distribution in control dogs (C), dogs suffering from food responsive diarrhea (FRD) or from inflammatory bowel disease (IBD)

Breed	C	FRD	IBD
Beagle	7	–	–
Bernese Mountain Dog	–	3	–
German Shepherd	6	3	2
Rotweiler	4	1	1
Mixed breed	–	3	2
Labrador Retriever	3	2	–
Golden Retriever	2	2	–
Collie	2	–	–
Malinois	2	2	–
Dachshound	1	–	2
Border Collie	1	1	–
Chihuahua	–	1	–
Great Dane	1	1	–
Landseer	–	1	–
Leonberger	–	1	–
West Highland White Terrier	–	1	–
Whippet	–	1	–
Appenzell Cattle Dog	1	–	–
Beauceron	1	–	–
Boxer	1	–	1
Canadian Shepherd	1	–	–
German Wire-haired Pointing Dog	1	–	–
Doberman Pinscher	1	–	–
Flat Coated Retriever	1	–	–
Bavarian Mountain Scenthound	1	–	–
Gorden Setter	1	–	–
Hovawart	1	–	–
Husky	1	–	–
Poodle	1	–	–
Setter	1	–	–
Mastiff	–	–	1
Coton de Tuléar	–	–	1
Sharpei	–	–	1

Blood samples

Blood (2–5 ml) was taken either from the cephalic vein, saphenic vein or jugular vein and collected into tubes containing dipotassium-EDTA (1.8 mg/ml blood) at the day of endoscopy. Samples were put on ice until centrifugation at 2 000 × g for 20 minutes. Plasma was aliquoted and stored at –20°C.

Laboratory analyses

Plasma IGF-1 was measured by radioimmunoassay (RIA) shown to be suitable for dogs (Blum et al., 1992; Zentek et al., 2003). Plasma concentrations of total protein, albumin, glucose, and urea were measured using kits (#193 7093, #822 7134, #813 0536, and #150 7326, respectively) of the VetTest 8008, IDEXX Laboratories, Westbrook Maine, USA.

Non-esterified fatty acids (NEFA) in plasma were measured with a kit from Wako Chemicals, Neuss, Germany (#994-75409).

Haptoglobin concentrations were measured by competitive enzyme-linked immuno sorbent assay (ELISA) with polyclonal antibodies raised in rabbits as described by Hiss (2001). Purified canine haptoglobin was used as standard. The limit of detection was 0.04 µg/ml, intra- and interassay coefficients of variation were 2% (based on 5 tests) and 11% (based on 14 tests), respectively.

Statistical analysis

The BW, age, CIBDAI, and metabolic trains are expressed as means ± upper and lower range or SEM. Values of haptoglobin are expressed as mean ± upper and lower 95% confidence level. Data were analyzed with the NCSS software package 2001 (Kaysville, UT). The level of significance was set at $P < 0.05$ and the level of trend was set at $P < 0.1$. Correlations of IGF-1 plasma concentration with BW and age were calculated by Spearman's rank correlation test. Because IGF-1 concentrations were closely dependent on BW (more details are given in the result-part), they were adjusted for BW and for further analysis the ratio IGF-1/BW was used. Differences in IGF-1/BW between males and females were analyzed with Wilcoxon Signed-Rank Test. Differences of IGF-1/BW, TP, albumin, glucose, urea, NEFA, and haptoglobin between FRD^{bef}, IBD^{bef} and C, respectively and between FRD^{aft}, IBD^{aft} and C, were analyzed by the Kruskal Wallis ANOVA on Ranks with Bonferroni correction for multiple comparisons. Differences in BW, IGF-1/BW, TP, albumin, glucose, urea, NEFA, haptoglobin and CIBDAI between IBD^{bef} and IBD^{aft} or between FRD^{bef} and FRD^{aft} were identified using the Wilcoxon Signed-Rank Test. Correlations of IGF-1/BW or haptoglobin with CIBDAI were analyzed by Spearman's rank correlation test.

RESULTS

Health status

The clinical condition of sick dogs improved during the treatment period in FRD and IBD dogs and CIBDAI decreased in both groups [FRD^{bef}: 6 ± 0.5 (range 2 to 8), FRD^{aft}: 1 ± 0.2 (range 0 to 3) ($P < 0.001$); IBD^{bef}: 8 ± 0.4 (range 6 to 9), IBD^{aft}: 5 ± 1.1 (range 0 to 10) ($P < 0.05$)]. There were no differences in BW before and after treatment.

Metabolites and haptoglobin (Table 2)

Concentration of plasma glucose was lower in dogs with FRD^{bef} than in C ($P < 0.05$). Plasma NEFA concentration was significantly lower in C than in

Table 2. Plasma concentration of glucose, total protein (TP), albumin, urea, non-esterified fatty acids (NEFA), and haptoglobin

Trait*	C	FRD^{bef}	FRD^{aft}	IBD^{bef}	IBD^{aft}	Group effect[a]
Glucose (mmol/l)	5.6 ± 0.3	5.1 ± 0.2	5.2 ± 0.4	5.2 ± 0.3	5 ± 0.2	$P < 0.05$
TP (g/l)	57.4 ± 6	61.1 ± 1	63.8 ± 1.2	60.1 ± 2.4	57.3 ± 5	NS
Albumin (g/l)	36.3 ± 0.9	35.3 ± 0.7	35.5 ± 1.01	32.8 ± 1.7	31.8 ± 3	NS
Urea (mmol/l)	5.9 ± 0.5	6.4 ± 0.4	6 ± 0.4	5.6 ± 0.8	6.1 ± 0.9	NS
NEFA (mmol/l)	0.9 ± 0.1	1.4 ± 0.1	1.5 ± 0.1	1 ± 0.1	1.2 ± 0.1	$P < 0.001$
Haptoglobin (g/l)	1.8 (0.8–2.8)	1.3 (0.8–1.8)	1.3 (0.8–1.7)	3 (1.2–4.7)	4.8 (0.4–9.2)	$P < 0.05$

C = healthy control dogs, FRD^{bef} = dogs suffering from food responsive diarrhea before treatment, FRD^{aft} = dogs suffering from food responsive diarrhea after treatment, IBD^{bef} = dogs suffering from inflammatory bowel disease before treatment, IBD^{aft} = dogs suffering from inflammatory bowel disease after treatment

*mean value ± SEM (standard error of the mean), respectively ± upper and lower 95% confidence level for haptoglobin concentrations

[a]Kruskal Wallis test: glucose: $FRD^{bef} < C$; NEFA: FRD^{bef} and $FRD^{aft} > C$; haptoglobin: $IBD^{bef} > C$, FRD^{bef}, $IBD^{aft} > FRD^{aft}$ and C

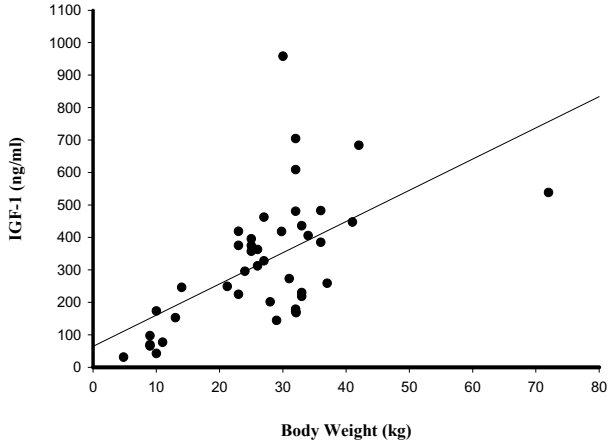

Figure 1. Relationship between body weight and plasma IGF-1 concentration in healthy dogs (C) (r_{sp} = 0.6; P < 0.001)

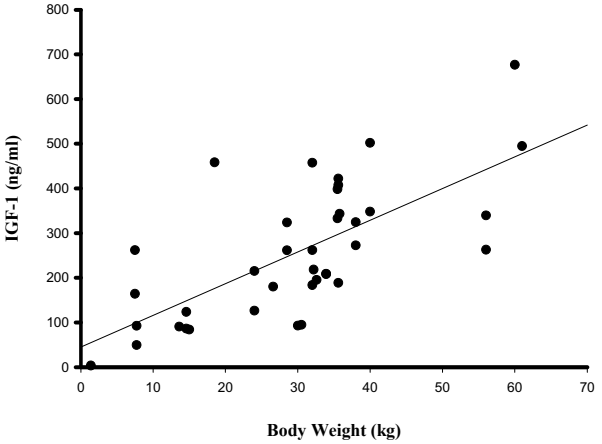

Figure 2. Relationship between body weight and plasma IGF-1 concentration in dogs with FRD (r_{sp} = 0.7; P < 0.001)

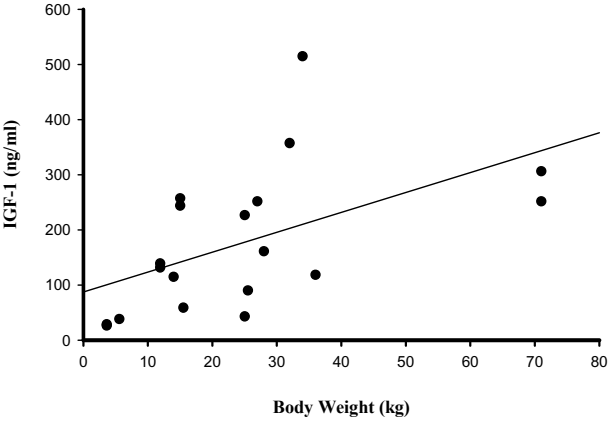

Figure 3. Relationship between body weight and plasma IGF-1 concentration in dogs with IBD (r_{sp} = 0.7; P < 0.05)

FRD^{bef} and FRD^{aft} (P < 0.001). Plasma concentrations of total protein, albumin and urea did not differ among C, FRD and IBD. Haptoglobin plasma concentrations were higher in IBD^{bef} than in FRD^{bef} and C; and higher in IBD^{aft} than in FRD^{aft} and C (P < 0.05). The correlation between CIBDAI score and haptoglobin was low (r = 0.3, P < 0.05), however haptoglobin concentrations were increased in dogs having moderate to severe gastrointestinal symptoms: 1.8 g/l (confidence level 0.7–3.0 g/l) in CIBDAI scores ≤5 and 2.5 g/l (confidence level 1.6–3.5 g/l) in CIBDAI scores >5 (P < 0.05).

IGF-1

Plasma IGF-1 concentrations were significantly correlated with BW in C, FRD, and IBD (Figures 1, 2, 3). There were no significant correlations between IGF-1 concentration and age (r_{sp} = –0.2) and between IGF-1/BW and CIBDAI. Gender had no significant influence on the IGF-1/BW ratio. The IGF-1/BW ratios were not significantly correlated with age.

Ratios of IGF-1/BW were lower in FRD^{bef} and IBD^{bef} than C (P < 0.01) (Figure 4). The IGF-1/BW ratio was higher in FRD^{aft} than FRD^{bef} (P < 0.05), but was not significantly higher in IBD^{aft} than IBD^{bef} (Figure 5). Ratios of IGF-1/BW were similar in FRD^{aft}, IBD^{aft} and C.

DISCUSSION

As shown by Allenspach and Gaschen (2003), gastrointestinal signs of dogs with CE improved after treatment with an elimination diet either combined with prednisolone (in dogs with IBD) or without

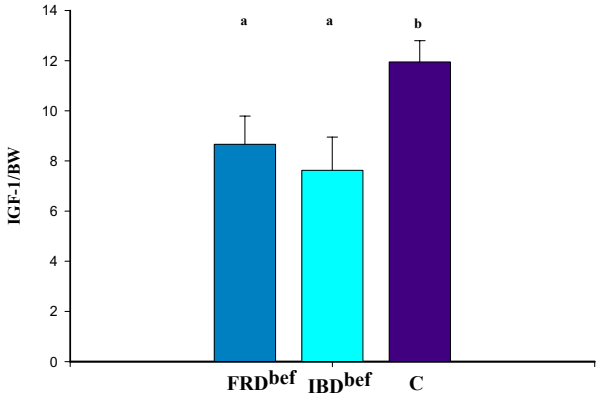

Figure 4. IGF-1/BW in FRD^{bef}, IBD^{bef} and healthy dogs (C)

a, b = different letters indicate significant differences between groups ($P < 0.01$)

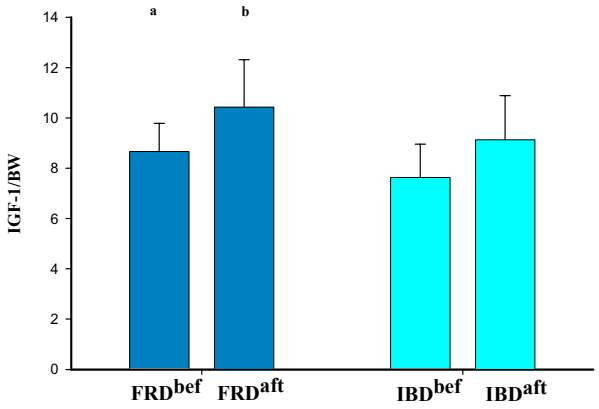

Figure 5. Comparison of IGF-1/BW in FRD and IBD dogs before and after treatment

a, b = different letters indicate significant differences between groups ($P < 0.05$)

prednisolone (in dogs with FRD). Improvement was additionally confirmed by significantly decreased CIBDAI scores. In order to have an additional and objective marker of the severity of intestinal inflammation, we measured plasma concentrations of haptoglobin, a member of the family of acute phase proteins (Murata et al., 2004). In contrast to earlier studies (Jergens et al., 2003), haptoglobin levels and CIBDAI scores were poorly correlated. However, levels of haptoglobin were higher in IBD dogs than in all other dogs, in accordance with highest CIBDAI scores in IBD dogs, indicating a moderate acute phase response. These findings are in agreement with results previously described by Sauter et al. (2005a) who demonstrated an acute phase response in IBD dogs based on enhanced expression of tumor necrosis factor-α in the duodenum. Haptoglobin concentrations were still elevated in IBD dogs after treatment. Prednisolone treatment is known to increase haptoglobin levels in dogs (Harvey and West, 1987; Martinez-Subiela et al., 2004). However prednisolone treatment in IBD dogs was stopped at least 2 weeks prior to the second blood sampling. According to Martinez-Subiela et al. (2004) a period of two to three weeks is needed until glucocorticoid effects after continuous administration of prednisolone have disappeared. It remains open whether increased haptoglobin levels in post treatment samples reflect glucocorticoid interactions or still indicate an inflammatory response in these dogs.

Plasma IGF-1 concentrations of C, FRD and IBD in this study were closely correlated with BW. In accordance with our results, Eigenmann et al. (1984b) found a significant correlation between BW and plasma IGF-1 concentration in different sized poodles and dogs of other breeds. White et al. (1999) found a positive correlation between BW and serum IGF-1 concentration in growing Beagles and Great Danes. Positive associations between BW and plasma IGF-1 concentrations were also found in other animals, such as in beef cattle and pigs (Ronge and Blum, 1989; Tang et al., 1997). The dependency of plasma IGF-1 concentration on BW made it necessary to express IGF-1 data relative to BW.

In our study, IGF-1/BW ratios were significantly lower in dogs before treatment than in C. Gronbaek et al. (2002) and Corkins et al. (2003) also found decreased plasma concentrations of IGF-1 and IGFBP-3 (the protein that transports the bulk of plasma IGF-1) in humans with IBD. Similar results were found in gluten-sensitive Irish Setters during a gluten challenge (Maxwell et al., 1998b) and in pigs infected with *Salmonella enterica* serovar Typhimurium (Jenkins et al., 2004). Plasma IGF-1 concentration decreases in various forms of inflammations or infections, as shown in cattle, pigs, rats, and mice (Elsasser et al., 1998; Frost and Lang, 2004).

Our results show an increase of the IGF-1/BW ratio during treatment with either the elimination diet (FRD) alone or the diet combined with glucocorticosteroids (IBD), although there was only in FRD dogs a significant time effect. The increase was associated with a strongly improved clinical status,

as confirmed by the CIBDAI scoring. The insignificant increase of the IGF-1/BW ratio in IBD dogs over time may in part be explained by the higher CIBDAI scores in these dogs than in FRD dogs. Furthermore, IBD dogs were additionally treated with glucocorticoids and it is known that long term glucocorticoid treatment reduces plasma IGF-1 concentrations (Hammon et al., 2003). However, prednisolone treatment of IBD dogs was stopped at least 2 weeks prior to the first and second blood sampling, as discussed for haptoglobin. Therefore we suppose that glucocorticoid treatment was not responsible for decreased plasma IGF-1/BW ratios. Our data agree with Gronbaek et al. (2002), who found an increase of serum IGF-1 concentrations in human patients with IBD towards levels in healthy controls after 12 weeks of treatment with high doses of prednisolone. Corkins et al. (2003), too, showed an increase of initially reduced IGF-1 levels at remission in children with IBD.

The IGF axis is responsive to changes in energy and protein balances, as reviewed by Thissen et al. (1994) and as also shown in dogs (Blum et al., 1992; Zentek et al., 2003) and various other species. Dogs with CE are expected to have a reduced energy and possibly protein balance because of reduced appetite, likely reduced digestion and intestinal absorptive capacities and probably enhanced energy and protein requirements due to enhanced immune responses. This could at least partly explain the decreased IGF-1 plasma levels in dogs with CE. Therefore plasma concentrations of glucose, total protein, albumin, urea and NEFA were measured as indicators of the metabolic status of the animals. Plasma concentrations of glucose, total protein, albumin, and urea were all in the range of reference values of healthy dogs (Kraft and Dürr, 1999). Plasma NEFA concentration of C corresponded with levels in healthy dogs examined by Gayet et al. (2004), whereas values of FRD and IBD were higher and in the range of values in obese dogs, where enhanced lipolysis leads to increased plasma NEFA levels. The significantly lower glucose concentrations in FRD^{bef} than in C and the significantly lower NEFA levels in C than in FRD^{bef} and FRD^{aft} may indicate a reduced energy intake or enhanced energy requirements in FRD dogs, although the reduction in glucose concentration cannot be considered to be clinically important. However, there were no significant differences between C and IBD dogs. The significant difference in glucose and NEFA levels between FRD and C may indicate an age effect because FRD dogs were younger than C and IBD dogs and they might have responded more sensitively to the food withdrawal in preparation for endoscopy. Puppies of any breed are more likely to develop hypoglycemia than adult dogs (Hoskins et al., 2001) and restricted energy intake is followed by enhanced lipolysis, as also shown in dogs (Diez et al., 2004).

Because Maxwell et al. (1998a) showed that overnight fasting had no effect on IGF-1 or IGFBP-3 concentrations in dogs, whereas an energy intake below maintenance energy requirements for two weeks decreased IGF-1 concentrations, a rather long-lasting energy deficiency seems to be needed to reduce plasma IGF-1 levels. Our dogs underwent only a short fasting period in preparation for endoscopy and this procedure was therefore barely responsible for reduced plasma IGF-1 concentrations on first admission. Furthermore dogs underwent the same procedure in preparation for the second endoscopy. Reduced CIBDAI scores, suggesting that the health status of the GIT improved, likely followed by an improved energy and (or) protein status, were therefore most probably responsible for increased IGF-1/BW ratios after treatment. As shown earlier, re-feeding of previously energy-restricted dogs is associated with increased plasma IGF-1 levels (Eigenmann et al., 1985).

Cytokines play an important role in chronic inflammation and influence also the somatotropic axis. Wolf et al. (1996) and Katsanos et al. (2001) have shown that a systemic inflammatory condition is associated with hepatic growth hormone (GH) resistance due to a suppression of hepatic GH receptor synthesis induced by inflammatory cytokines. Fan et al. 1995, 1997) found reduced plasma concentrations of IGF-1 in fasted rats after infusion of murine tumor necrosis factor-α and interleukin-1β. De Benedetti et al. (1997) demonstrated a decrease in circulating IGF-1 in association with an overproduction of interleukin-6. Elsasser et al. (2000) showed that during infectious stress, cytokines like tumor necrosis factor-α can up-regulate the production of nitrogen free radicals which can block otherwise normal biochemical processes that regulate cell function, as for example the regulation of IGF-1 production by GH. This down-regulation of hepatic GH receptors leads to a decrease in plasma IGF-1 levels. Based on that, the reduced plasma IGF-1 concentrations in dogs with CE before treatment were likely, too, associated with enhanced expression of inflammatory cytokines in the GIT (Sauter et al., 2005a).

In conclusion, IGF-1/BW ratios were significantly lower in dogs with FRD and IBD than in healthy dogs and increased during treatment. Therefore, determination of the IGF-1/BW ratio can basically help to judge the recovery process of dogs suffering from CE.

REFERENCES

Allenspach K., Gaschen F. (2003): Chronische Darmerkrankung beim Hund: Eine Uebersicht. Schweizer Archiv fur Tierheilkunde, 145, 209–222.

Allenspach K., Luckschander N., Styner M., Seibold F., Doherr M., Aeschbach D., Gaschen F. (2004): Evaluation of assays for perinuclear antineutrphilic cytoplasmatic antibodies and antibodies to *Saccharomyces cerevisiae* in dogs with inflammatory bowel disease. American Journal of Veterinary Research, 65, 1279–1283.

Baxter R.C. (2001): Changes in the IGF-IGFBP axis in critical illness. Best Practice and Research: Clinical Endocrinology and Metabolism, 15, 421–434.

Beattie R.M., Camacho-Hubner C., Wacharasindhu S., Cotterill A.M., Walker-Smith J.A., Savage M.O. (1998): Responsiveness of IGF-I and IGFBP-3 to therapeutic intervention in children and adolescents with Crohn's disease. Clinical Endocrinology, 49, 483–489.

Blum J.W., Zentek J., Meyer H. (1992): The effect of a different energy supply on the growth intensity and skeletal development of growing Great Danes 2. Effect on insulin-like growth factor I and on thyroid hormones. Zentralblatt Veterinarmedizin A, 39, 568–574.

Corkins M. R., Gohil A.D., Fitzgerald J.F. (2003): The insulin-like growth factor axis in children with inflammatory bowel disease. Journal of Pediatric Gastroenterology and Nutrition, 36, 228–234.

De Benedetti F., Alonzi T., Moretta A., Lazzaro D., Costa P., Poli V., Martini A., Ciliberto G., Fattori E. (1997): Interleukin-6 causes growth impairment in transgenic mice through a decrease in insulin-like growth factor-I. A model for stunted growth in children with chronic inflammation. Journal of Clinical Investigations, 99, 643–650.

Diez M., Michaux C., Jeusette I., Baldwin P., Istasse L., Biourge V. (2004): Evolution of blood parameters during weight loss in experimental obese Beagle dogs. Journal of Animal Physiology and Animal Nutrition, 88, 166–171.

Eigenmann J.E., Patterson D.F., Zapf J., Froesch E.R. (1984a): Insulin-like growth factor I in the dog: a study in different dog breeds and in dogs with growth hormone elevation. Acta Endocrinologica, 105, 294–301.

Eigenmann J.E., Patterson D.F., Froesch E.R. (1984b): Body size parallels insulin-like growth factor I levels but not growth hormone secretory capacity. Acta Endocrinologica, 106, 448–453.

Eigenmann J.E., Bruijne J.J., Froesch E.R. (1985): Insulin-like growth factor I and growth hormone in canine starvation. Acta Endocrinologica, 108, 161–166.

Elsasser T.H., Kahl H., Steele N.C., Rumsey T.S. (1997): Nutritional modulation of somatotropic axis-cytokine relationships in cattle: a brief review. Comparative Biochemistry and Physiology part A, 116, 209–221.

Elsasser T.H., Sartin J.L., McMahon C., Romo G., Fayer R., Kahl S., Blagburn B. (1998): Changes in somatotropic axis response and body composition during growth hormone administration in progressive chachectic parasitism. Domestic Animal Endocrinology, 15, 239–255.

Elsasser T. H., Kahl S., Rumsey T. S, Blum J. W. (2000): Modulation of growth performance in disease: reactive nitrogen compounds and their impact on cell proteins. Domestic Animal Endocrinology, 19, 75–84.

Fan J., Char D., Bagby G.J., Gelato M.C., Lang C.H. (1995): Regulation of insulin-like growth factor I (IGF-I) and IGF-binding proteins by tumor necrosis factor. American Journal of Physiology, 269, R1204–R1212.

Fan J., Wojnar M.M., Theodorakis M., Lang C.H. (1997): Regulation of insulin-like growth factor (IGF)-I mRNA and peptide and IGF-binding proteins by interleukin-1. American Journal of Physiology, 270, R621–R629.

Frost R.A., Lang C.H. (2004): Alteration of somatotropic function by proinflammatory cytokines. Journal of Animal Science, 82, 100–109.

Gayet C., Bailhache E., Dumon H., Martin L., Siliart B., Nguyen P. (2004): Insulin resistance and changes in plasma concentration of TNF-alpha, IGF-1, and NEFA in dogs during weight gain and obesity. Journal of Animal Physiology and Animal Nutrition, 88, 157–165.

Gronbaek H., Thogersen T., Frystyk J., Vilstrup H., Flyvbjerg A., Dahlerup J.F. (2002): Low free and total insulin like growth factor I (IGF-I) and IGF binding rotein-3 levels in chronic inflammatory bowel disease: Partial normalization during prednisolone treatment. American Journal of Gastroenterology, 97, 673–678.

Hammon H.M., Zbinden Y., Sauerwein H., Breier B.H., Blum J.W., Donkin S.S. (2003): The response of the hepatic insulin-like growth factor system to growth hormone and dexamethasone in calves. Journal of Endocrinology, 179, 427–435.

Harvey J.W., West C.L. (1987): Prednisone-induced increases in serum alpha-2-globulin and haptoglobin concentrations in dogs. Veterinary Pathology, 24, 90–92.

Hiss S. (2001): Entwicklung und Validierung von enzymimmunologischen Messverfahren zur Bestimmung von Haptoglobin bei verschiedenen Haustierspezies und erste Anwendungen in Pilotstudien. [Diss. med. vet.]. Shaker Verlag, Aachen. ISBN 3-8265-9010-4.

Hoskins J.D. (2001): Hypoglycemia in puppies. In: Veterinary Pediatrics: Dogs and Cats from Birth to Six Months. 3rd ed. WB Saunders Co., Philadelphia. 361–370.

Jenkins N.L., Turner J.L., Dritz S.S., Durham S.K., Minton J.E. (2004): Changes in circulating insulin-like growth factor binding proteins, and leptin in weaned pigs infected with *Salmonella enterica* serovar Typhimurium. Domestic Animal Endocrinology, 26, 49–60.

Jergens A.E., Schreiner C.A., Frank D.E., Niyo Y., Ahrens F.E., Eckersall P.D., Benson T.J., Evans R. (2003): A scoring index for disease activity in canine inflammatory bowel disease. Journal of Veterinary Internal Medicine, 17, 291–297.

Katsanos K.H., Tsatsoulis A., Christodoulou D., Challa A., Katsaraki A., Tsianos E.V. (2001): Reduced serum insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 levels in adults with inflammatory bowel disease. Growth Hormone & IGF Research, 11, 364–367.

Kraft W., Dürr U.M. (1999): Referenzbereiche. In: Klinische Labordiagnostik in der Tiermedizin. 5th ed. Schattauer, Stuttgart, New York. 344–359.

Martinez-Subiela S., Ginel P.J., Ceron J.J. (2004): Effects of different glucocorticoid treatments on serum acute phase proteins in dogs. Veterinary Record, 154, 814–817.

Maxwell A., Butterwick R., Yateman M., Batt R.M., Cotterill A., Camacho-Hubner C. (1998a): Nutritional modulation of canine insulin-like growth factors and their binding proteins. Journal of Endocrinology, 158, 77–85.

Maxwell A., Elwood C.M., Garden O., Camacho-Hubner C., Batt R.M. (1998b): Insulin-like growth factor axis of gluten-sensitive dogs during a gluten challenge. Veterinary Record, 143, 68–71.

Murata H., Shimada N., Yoshioka M. (2004): Current research on acute phase proteins in veterinary diagnosis: an overview. Veterinary Journal, 168, 28–40.

Ronge H., Blum J.W. (1989): Insulin-like growth factor I during growth in bulls. Reproduction, Nutrition, Development, 29, 105–111.

Sauter S.N., Allenpach K., Gaschen F., Ontsouka E., Benyacoub J., Blum J.W. (2005a): Cytokine expression patterns in intestinal samples of dogs suffering from chronic inflammatory bowel disease. In: Proceedings, 59th Annual Meeting of the Society Nutrition and Physiology, 14, 152.

Sauter S.N., Allenspach K., Gaschen F., Grone A., Ontsouka E., Blum J.W. (2005b): Cytokine expression in an ex vivo culture system of duodenal samples from dogs with chronic enteropathies: Modulation by probiotic bacteria. Domestic Animal Endocrinology, 29, 605–622.

Tang M., Van Kessel A.G., Laarveld B. (1997): Insulin growth factor-1 in weanling growing pigs. Ontogeny of serum insulin-like growth factor-1 in pigs form birth to 65 days of age. Available at: www.aginfonet.com/agilibrary/content/prairie_swine_centre/95swine_insulin.html

Thissen J.P., Ketelslegers J.M., Underwood L.E. (1994): Nutritional regulation of insulin-like growth factors. Endocrine Reviews, 15, 80–101.

White M.E., Hathaway M.R., Dayton W.R., Henderson T., Lepine A.J. (1999): Comparison of insulin-like growth factor-I concentration in mammary secretions and serum of small- and giant-breed dogs. American Journal of Veterinary Research, 60, 1088–1091.

Wolf M., Bohm S., Brand M., Kreymann G. (1996): Pro-inflammatory cytokines interleukin-1 beta and tumor necrosis factor-alpha inhibit growth hormone stimulation of insulin-like growth factor I synthesis and growth hormone receptor mRNA levels in cultured rat liver cells. European Journal of Endocrinology, 135, 729–737.

Zentek J., Stephan I., Kramer S., Gorig C., Blum J.W., Mischke R., Nolte I. (2003): Response of dogs to short-term infusions of carbohydrate- or lipid-based parenteral nutrition. Journal of Veterinary Medicine series A, 50, 313–321.

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