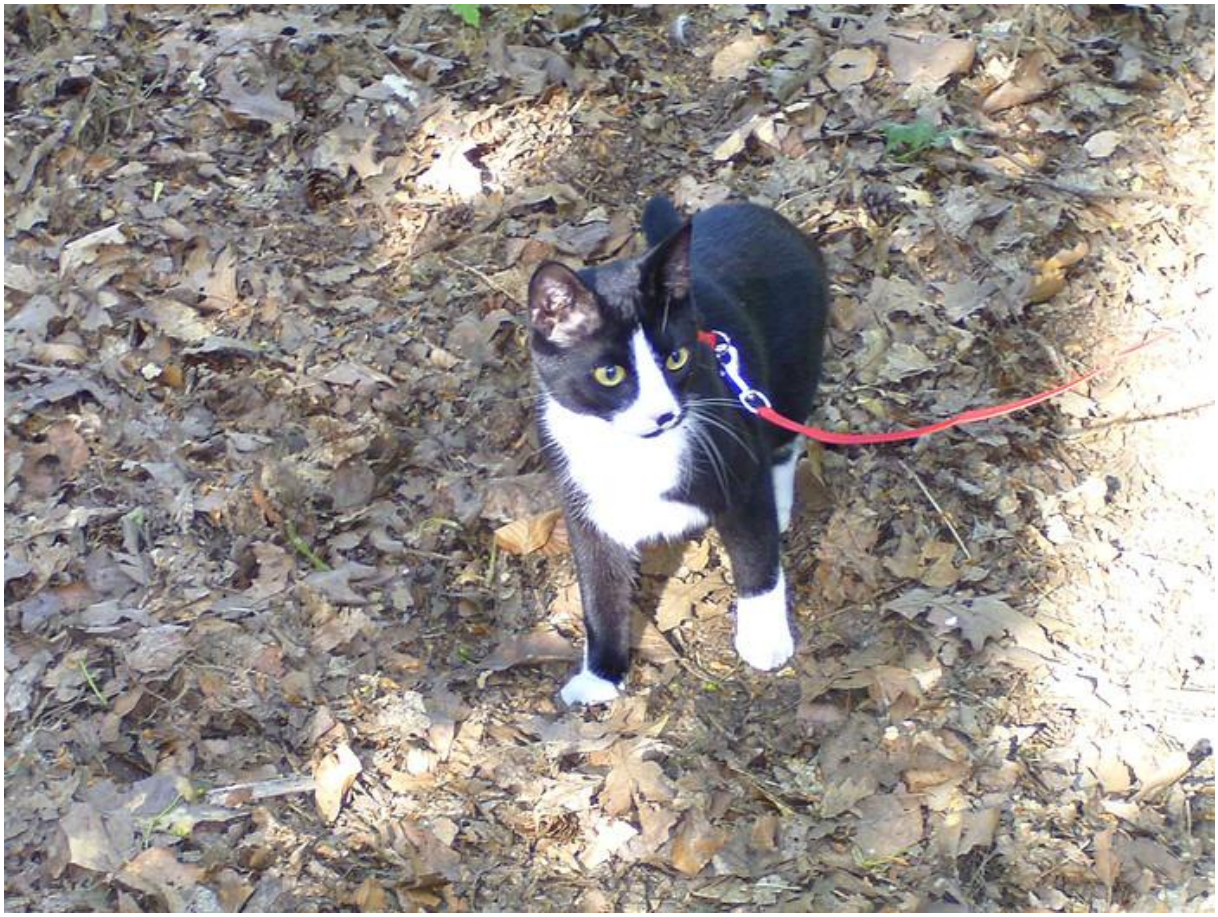
Prevalence of acromegaly in cats with diabetes mellitus in the Netherlands



Research Project Veterinary Medicine Utrecht University

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Prefatory note

Within the training of veterinary medicine at the Utrecht University, all students have to fulfill a research project. This paper is the final report of the research project carried out by J. Faas at the department of clinical sciences of companion animals of the university of Utrecht.

Research was carried out to get to know more about the of acromegaly in cats affected by diabetes mellitus.

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Summary

Diabetes mellitus affects about 2% of the cat population in all countries. According to the literature 80-95% is affected by type II diabetes mellitus, and 5-20% by type III diabetes mellitus, caused by underlying conditions. The aim of this study was to investigate the prevalence of acromegaly in diabetic cats. For a long time, acromegaly was considered a very rare condition in cats, but recent studies have shown percentages up till 32% with elevated insulin-like growth factor-I, an indicator for acromegaly. Diabetic cats were clinically examined and, blood and urine samples were taken.

21-31% of 123 examined cats had elevated IGF-1 concentrations in the blood, depending on the cut off value used for elevated IGF-1 (1000 vs 800 µg/l). No correlation was found between plasma IGF-1 concentration and plasma fructosamine concentration. There was a correlation between insulin dose and IGF-1 concentration, indicating difficult glycemic control in acromegaly. Difficult glycemic control is known in acromegaly cats, because of induced insulin resistance.

Introduction

Diabetes Mellitus in cats

Diabetes mellitus (DM) is a condition characterized by an insufficient amount of insulin. Diabetes mellitus is described in several kinds of mammals.

Different types of diabetes mellitus are known, all with a different cause.

DM type I is characterized by auto-immune damage of the β-cells in the Islets of Langerhans. This type of diabetes is rarely seen in cats.

DM type II originates from a combination of development of insulin resistance and a decrease in insulin supply. Insulin resistance is caused by obesitas and physical inactivity. Increased workload of the β-cells of the Islets of Langerhans leads to exhaustion and to hydropic degeneration of these cells. In cats, the β-cells can be damaged by the formation of amyloid in the islets of Langerhans. Most cats with DM are affected by type II.

DM type III is caused by underlying conditions. Many conditions are known to cause DM in cats: acromegaly, Cushing's syndrome, pancreatitis, exocrine pancreas neoplasia and renal failure. All these conditions lead to insulin resistance. Exogenous progestagens or glucocorticoids may also cause type III DM. These hormones cause an increase in the gluconeogenesis and causes insulin resistance.

DM type IV is seen with pregnancies. The placenta generates hormones that cause insulin resistance. B-cells can compensate until a certain level of insulin resistance has developed, after which DM develops. This type of DM is unknown in cats.

Cats are often diagnosed at an age between 10 and 13 years. Clinical signs are polyuria, polydipsia, polyphagia and weightloss. When the DM is complicated by ketoacidosis additional clinical signs as anorexia, vomiting, diarrhea, lethargy and weakness can develop.

Laboratory findings include glucosuria, ketonuria and hyperglycemia. An ongoing DM can cause hyponatremia, hypokalemia and hypophosphatemia. When DM is caused by fatty degeneration of the liver, an increase in liver enzymes is found.

Diagnosis is based on glucosuria and persisting hyperglycemia. In cats hyperglycemia can also be caused by stress. Differentiation can be made by measurement of plasma fructosamine concentration. Fructosamine develops from the glycation of albumin.

With increasing obesitas in cats, DM is an upcoming disease. Burmese cats seem to be predisposed, as shown in research in Australia, New-Zealand and Great-Brittain.[1] (RAND)

Therapy consists of solving the underlying problem. Cats affected by DM are treated with insulin. Insulin is given subcutaneous, based on weight and concentration of glucose in blood. In the Netherlands, Caninsulin is used most often, and needs to be administered twice daily. When obesitas and physical activity as major causes, these are also part of therapy. There are indications that a diet

with low carbohydrates increases the change of disappearance of DM. In 25% an adequate therapy with insulin, dietary precautions, weight loss and stimulation of physical activity, lead to a disappearance of the DM.[1] (RAND)

0,5-2% of all cats suffer from DM, of which about 80-95% with type II, and 5-20% with type III, as former research in New-Zealand, Australia and Great-Brittain shows.[1] (RAND)

Acromegaly

Acromegaly is a rare condition in cats, but cats with acromegaly are almost always affected by DM. they are difficult to set at a certain amount of insulin.[2,3] (NIESSEN, HURTY) In a former research with cats with different glycemic control, 32% had elevated levels of IGF-1.[4] (SCOTT)

Acromegaly is caused by a functional somatotropic adenoma in the pars distalis of the anterior pituitary gland. This adenoma causes an excessive secretion of growth hormone (GH).[2,3,4,] (NIESSEN, HURTY, SCOTT)

In healthy cats GH is secreted in a pulsatile way by the pars distalis of the pituitary gland. There are negative feedback control mechanisms, which act at the level of the hypothalamus and pituitary. In cats with a pituitary adenoma these feedback mechanisms are disturbed which causes hypersomatotropism. This leads to an increase in frequency, duration and amplitude of the GH pulse. Acromegaly results from an overexposure to GH and insulin-like growth factor 1 (IGF-1). IGF-1 is produced in the liver, in the presence of GH. GH has anabolic and catabolic effects, IGF-1 has anabolic effects and together they cause the clinical signs.[2,3] (NIESSEN, HURTY)

GH is a modulator of insulin sensitivity. In the presence of hyperinsulinaemia, there is a reduction in insulin receptor levels and decrease of insulin kinase activity. GH causes insulin resistance mainly in striated muscle and in the liver.[2] (NIESSEN)

IGF-1 has an anabolic action, thus elevation for longer periods can lead to excessive growth of tissue and development of deformations. This can cause renal changes, myocardial changes, thyroid enlargement, adrenomegaly, hepatomegaly, thickening of oropharyngeal tissues, bone and cartilage remodeling and thickening. Renal changes can lead to renal failure. Myocardial changes can lead to congestive heart failure.[2,3,4](NIESSEN, HURTY, SCOTT)

Cats with acromegaly are often neutered males of middle to older age. Most cats are domestic shorthairs. Owners most report polyuria, polydipsia, polyphagia, weight gain and lameness. Other clinical signs include central nervous system signs, increase in paw size, changes in facial appearance and enlargement of the abdomen. On clinical examination hepatomegaly, enlargement of the kidneys, changes in facial appearance, respiratory stridor, prognathia inferior, lameness, systolic cardiac murmur, enlarged paws and central nervous system signs.[2,3,4] (NIESSEN, HURTY, SCOTT)

Laboratory findings only includes elevated total protein levels, when compared with DM. cats with increased renal reabsorption can have a hyperphosphataemia. Plasma IFG-1 concentration does not give a definite diagnosis, because false positive and negative results are known.[2,3] (NIESSEN, HURTY)

When IGF-1 levels suggest acromegaly, intracranial imaging by CT-scan or MRI can be done to confirm the diagnosis.[2,3,4] (NIESSEN, HURTY, SCOTT)

Therapy consist of hypophysectomy at the University of Utrecht. This is a highly specialized procedure.[2] After hypophysectomy not only the acromegaly is gone but almost always there is also remission of DM.(NIESSEN) In other countries radiotherapy is used. Not all cats respond well and there are also disadvantages. There is a need for multiple anaesthesias, an unpredictable response and minor side-effects, like depigmentation. Also, costs can be a disadvantage.[2,3,4] (NIESSEN, HURTY, SCOTT).

Cats with insulin resistance show signs of difficult glycemic control, which include polyuria, polydipsia, polyphagia, weight loss and peripheral neuropathy. Cats with these clinical signs and insulin doses greater than 1.5U/kg (6 U per dose) are insulin resistant. These cats also have persistent hyperglycemia, and increased fructosamine concentrations.[4] (SCOTT)

Aim of this study

The aim of this study was to get to know more about the prevalence of acromegaly in diabetic cats. In the Netherlands this wasn't investigated in former studies. This research project was part of a big research project for the prevalence of all underlying conditions of DM in cats, in cooperation with a research project in Switzerland.

The second aim of this study was to investigate a correlation between elevated plasma levels of IGF-1 and fructosamine for an early diagnosis of acromegaly in diabetic cats.

Materials and methods

Letters were sent to veterinary practices in the Netherlands to inform practitioners about this research project and to ask for cooperation. The practitioners contacted the owners of diabetic cats about this research project. By permission of the cats owners the researcher contacted the owners to inform them about this research and make an appointment for examination and blood taking of the cat.

Cats were examined in their own veterinary practice. Owners were asked to collect urine from the cat, preferably morning urine. Before examination a questionnaire was answered by the owners. In this questionnaire questions about food and water intake, urinating, skin and coat condition, vomiting, diarrhea, locomotion, vision, nervous system and general functioning of the cat. Insulin doses and date of diagnosis of the diabetes were recorded. Before clinical examination all cats were weighed.

On examination cats were scored on a standardized form, used by all researchers. General impression was recorded from all cats. Head, neck, lymph nodes, skin, coat, thoracic cavity, abdominal cavity, mammae, locomotion, nervous system and thyroid gland of all cats were examined.

After general examination blood was taken from the vena jugularis. A total of 10 ml was taken, ideally, and separated in one EDTA tube and two serum tubes.

Processing of samples

At the veterinary diagnostic centre at the Utrecht University urine samples were investigated for specific gravity, pH, protein, hemoglobin, glucose, ketone bodies, cortisol and creatinine. Microscopic examination was done for leucocytes, erythrocytes, cylinders, epithelia, fat, calciumoxalate, struvite and bacteria.

Blood in the EDTA tube was investigated for hematocrit, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, leucocytes, lymphocytes, monocytes, blastocysts, mature and immature granulocytes, eosinophils, basophils and normocytes.

Serum tubes were averted and serum was transferred to small sample cups. These cups were frozen until transport to Switzerland.

The laboratory in Switzerland examined the serum for IGF-1, glucose, fructosamine, bilirubin, urea, creatinine, total protein, albumin, cholesterol, triglycerides, alkaline phosphatase, amylase, lipase, aspartate aminotransferase, alanine aminotransferase, sodium, potassium, chloride, calcium, phosphate and thyroxine.

Part of the serum was send to the United states of America for examination of feline pancreatic lipase immunoreactivity, feline trypsin-like immunoreactivity, folate and cobalamine.

Statistics

Results were analyzed in Microsoft Excel for percentages. SPSS was used to evaluate correlations and drawing graphics.

Results

Over 53 veterinary practices responded to the letters send. 123 owners and cats cooperated in this research project.

Mean age of 107 cats was 14,5 years. Mean weight of 107 cats was 7,3 kilograms.

31% of all cats had levels of IGF-1 above 800 ng/ml, the cut off value used in this research project. In other researches a cut off value above 1000 ng/ml is used. In this research project 21% of all cats would have elevated levels of IGF-1 if 1000 ng/ml would be used.

68% of all cats had fructosamine levels above normal for diabetic cats. Reference values for diabetic cats are different than for healthy cats. Of this 68% insufficient fructosamine, 12% was qualified as hypoglycemic. 32% of the cats had sufficient fructosamine levels. Fructosamine levels for these cats were qualified as excellent(12%), good(11%) and moderate(9%).

Of all cats with elevated IGF-1 levels when Utrecht references were used, 13% of cats had elevated fructosamine levels. Elevated IGF-1 and normal fructosamine was found in 10% of cats, and elevated IGF-1 with hypoglycemic fructosamine was found in 7,5%.

Of all cats with normal IGF-1 levels, 42% had elevated fructosamine levels, 22,5% had normal fructosamine levels and 5% had hypoglycemic fructosamine levels.

Of all cats with elevated IGF-1 levels when the normal references were used, 11,5% had elevated fructosamine levels, 5% had normal fructosamine and 4% had hypoglycemic fructosamine levels.

Of all cats with normal IGF-1 levels 44% had elevated fructosamine levels, 27,5% had normal fructosamine levels and 8% had hypoglycemic fructosamine levels.

Mean IGF-1 concentration was 715 ng/ml and mean fructosamine level was 512,5 µmol/l.

A correlation between IGF-1 and fructosamine was calculated with the Pearson's correlation test. There was a correlation of -0,136 with a significance of 0,15, so no correlation was found (Figure 1). 123 cats were used in the calculation of this correlation.

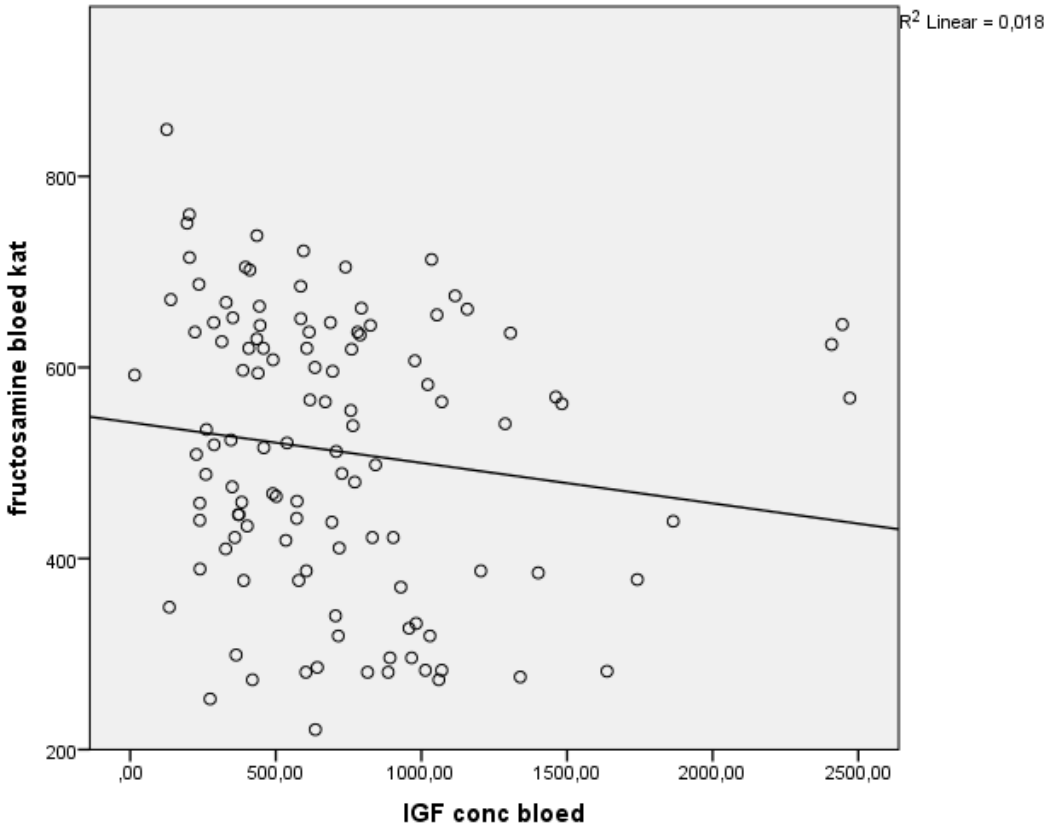

Figure 1

A correlation between IGF-1 concentration in blood and insulin dose given to the cats was also calculated. Insulin doses were known for 107 cats. Mean insulin dose of all cats was 6,2 IU. A correlation of 0,386 which was significant at a P-value of 0,01 (Figure 2).

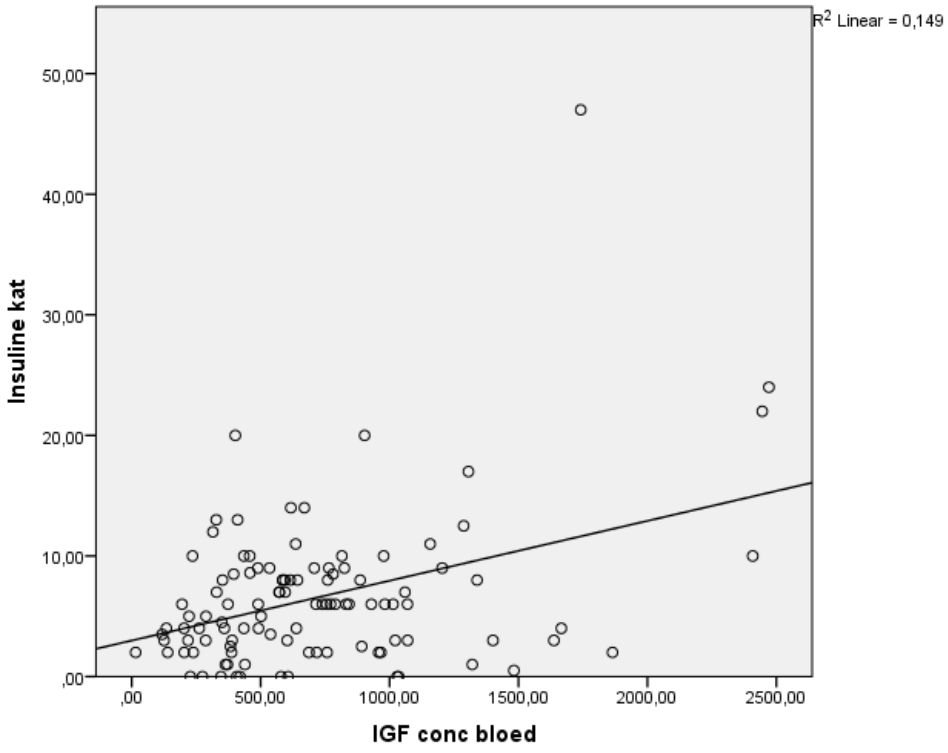

Figure 2

Discussion

In this research project veterinary practices and owners had to cooperate with the students of the university of Utrecht. Some owners may dislike the idea of students examining and taking blood of their cats. Owners with cats with difficult glycemic control may be more motivated to participate in this research, because all other underlying diseases causing DM were investigated. In a British investigation with different glycemic control cats, 32% was diagnosed with elevated IGF-1 levels. A cut off value of 1000 ng/ml was used. In this research at a cut off value of 1000 ng/ml, 21% had elevated IGF-1 levels. This is 10% less then found in research of Niessen et all.[5]

Elevated concentrations of fructosamine are caused by an inappropriate glycemic control. In almost all underlying conditions, glycemic control is difficult. A correlation between underlying diseases and elevated concentrations of fructosamine might be present, but is beyond the scope of this research.

This project was done in several provinces of the Netherlands, but not all provinces were approached by the students. Not all cooperating provinces had an equal amount of cats, as expected when distribution of people over all provinces was taken in to account.

In this research all cats were put in one group. To get better results it might be necessary to divide the cats in different groups, for example a group with good glycemic control, a group with healthy, non diabetic cats and a group of cats with difficult glycemic control. It is possible a positive correlation between difficult glycemic control and elevated levels of IGF-1 will then be found.

IGF-1 does not give a definit diagnosis in acromegaly, as stated in the introduction. CT-scans of all cats with elevated IGF-1 levels could confirm the diagnosis. With those results taken into account, a better statement for the prevalence of acromegaly in diabetic cats can be made. This is interesting for further research projects.

In this research we found a correlation between the insulin dose and IGF-1 levels. Research of Berg et all revealed no correlation between insulin dose and IGF-1 levels.[6] More research needs to be done to state a real existing or non-existing correlation.

Conclusion

21-31% of 123 examined cats had elevated IGF-1 concentrations in their blood. This is a strong indicator of acromegaly in cats, but is not definit.

No correlation was found between IGF-1 concentration and fructosamine concentration. There was a slight, non-significant, negative correlation.

There was a significant positive correlation between IGF-1 concentration and insulin dose given to the cats.

It would be the author's advice, to screen new cats with diabetes mellitus for underlying diseases.

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