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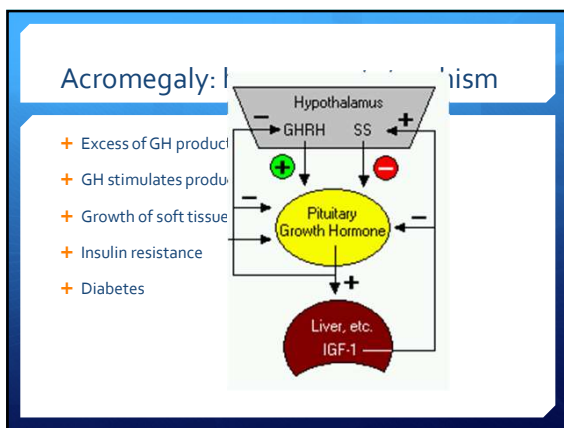
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### AIP gene mutations?

- + In humans most tumours are spontaneous
- + 20-40% familial (Primary genetic cause)
- + Feline acromegaly is similar to human familial acromegaly
  - + Male gender
  - + Macroadenoma somatotrophs
  - + Resistant to octreotide
- + Feline AIP gene: 6 exons - 330 AA
- + 98% homology with human AIP protein
- + DNA cats with acromegaly and controls

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### AIP in feline acromegaly?

- + Mutation in Exon 1
- + Glutamic-Aspartic aminoacid change



20%



0%

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Environment International 51 (2013) 66–67

Contents lists available at ScienceDirect  
**Environment International**  
 journal homepage: www.elsevier.com/locate/envint

Organohalogenated contaminants in domestic cats' plasma in relation to spontaneous acromegaly and type 2 diabetes mellitus: A clue for endocrine disruption in humans?

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ARTICLE INFO ABSTRACT

**Group 1: Acromegalic cats**  
**Group 2: Diabetic cats**  
**Group 3: Non-endocrine matched controls**

assess human exposure to chemicals present in indoor dust. © 2013 Elsevier Ltd. All rights reserved.

7



**Table 2.** Overview of the concentrations (mean, median, 10<sup>th</sup>, 25<sup>th</sup>, 75<sup>th</sup> and 90<sup>th</sup> percentile expressed in pg/mL) of persistent organic pollutants measured in serum samples collected from three groups of cats from the UK, sampled in 2010–2011.

	Group 1 (AC)	Group 2 (DC)	Group 3 (NC)
	(spontaneously induced diabetes)	(type 2 diabetes)	(age-matched controls)
PCB	1.2	1.1	1.0
PCB-153	1.1	1.0	0.9
PCB-180	1.0	0.9	0.8
PCB-194	0.9	0.8	0.7
PCB-203	0.8	0.7	0.6
PCB-207	0.7	0.6	0.5
PCB-219	0.6	0.5	0.4
PCB-229	0.5	0.4	0.3
PCB-237	0.4	0.3	0.2
PCB-246	0.3	0.2	0.1
PCB-254	0.2	0.1	0.0
PCB-267	0.1	0.0	0.0
PCB-276	0.0	0.0	0.0
PCB-283	0.0	0.0	0.0
PCB-292	0.0	0.0	0.0
PCB-300	0.0	0.0	0.0
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PCB-327	0.0	0.0	0.0
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### Role of organo-halogenates?

- Animals and humans are exposed through different routes
  - Food
  - Interior of houses
    - Dust ingestion
    - Cats washing themselves
- Comparable to feline hyperthyroidism
 

Dye 2007, Olczak 2005, Scarlett 1988

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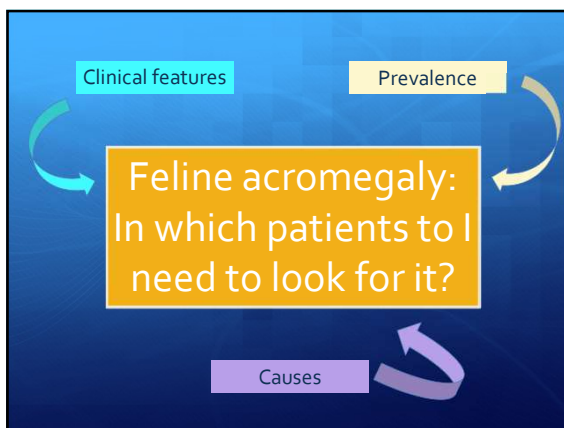
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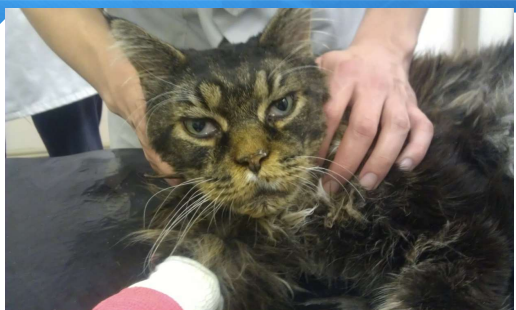
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### Acromegaly: clinical features



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### Acromegaly: epidemiology

- + More common in male cats
- + Average 11 years old
- + Breeds: DSH, Maine Coon, Burmese

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### Acromegaly: Clinical signs(2007)



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### Acromegaly: clinical signs

2007	2021
	
Diabetes with severe insulin resistance	
<ul style="list-style-type: none"><li>+ Weight gain</li><li>+ Respiratory stridor</li><li>+ Organomegaly</li><li>+ Broad paws</li><li>+ Broad facial features</li><li>+ HCM</li></ul>	<ul style="list-style-type: none"><li>+ Younger</li><li>+ Non-diabetic</li><li>+ Weight gain</li><li>+ Respiratory stridor</li><li>+ Normal facial features</li><li>+ No broad paws</li><li>+ HCM</li><li>+ Epilepsy</li></ul>

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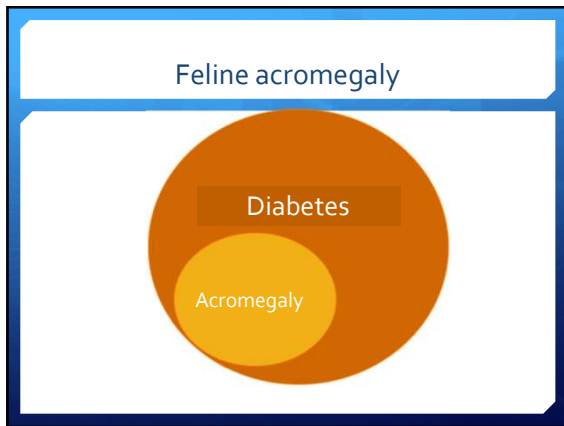
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### Feline acromegaly: Prevalence

- + 2007: Feline acromegaly has a relatively high prevalence in diabetic patients
- + 26-32% prevalence Niessen 2007, Berg 2007
- + Recently: several other prevalence studies
- + Schaefer (2013)
  -  + Niessen (2011) 

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### Prevalence



- + Schaefer abstract ECVIM Congress, JVIM, 2013
- + First opinion vets (Switzerland and Netherlands)
- + 1 in 5
- + [IGF-1] median 584
- + 17.8% IGF-1 > 1000 ng/ml

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## Prevalence

- + Free fructosamine measurement of diabetic cats
- + Leftover serum: IGF-1
- + Different assay
- + Cats had a free CT if IGF-1
- + N=1222
- +
- +

Different methodology

Different population

1 in 4



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## Evaluation of four methods used to measure plasma insulin-like growth factor 1 concentrations in healthy cats and cats with diabetes mellitus or other diseases

Flurin Tschuor, Dr med vet; Eric Zini, Dr med vet; Stefan Schellenberg, Dr med vet; Monique Wenger, Dr med vet; Felicias S. Boretti, Dr med vet; Claudia E. Reusch, Prof Dr med vet

**Objective**—To evaluate 4 methods used to measure plasma insulin-like growth factor (IGF) 1 concentrations in healthy cats and cats with diabetes mellitus or other diseases.

**Animals**—39 healthy cats, 7 cats with diabetes mellitus, and 33 cats with other diseases.

**Procedures**—4 assays preceded by different sample preparation methods were evaluated, including acid chromatography followed by radioimmunoassay (AC-RIA), acid-ethanol extraction followed by immunodometry assay (AEE-RMA), acidification followed by immunochemoluminescence assay (A-ICMA), and IGF-2 excess followed by RIA (IE-RIA). Validation of the methods included determination of precision, accuracy, and recovery. The concentration of IGF-1 was measured with all methods, and results were compared among cat groups.

**Results**—The intra-assay coefficient of variation was < 10% for AC-RIA, A-ICMA, and AEE-RMA and 14% to 22% for IE-RIA. The linearity of dilution was close to 1 for each method. Recovery rates ranged from 69% to 119%. Five healthy cats had IGF-1 concentrations > 1,000 ng/mL with the AEE-RMA, but < 1,000 ng/mL with the other methods. Compared with healthy cats, hyperthyroid cats had significantly higher concentrations of IGF-1 with the A-ICMA method, but lower concentrations with the IE-RIA method. Cats with lymphoma had lower IGF-1 concentrations than did healthy cats regardless of the method used.

**Conclusions and Clinical Relevance**—Differences in the methodologies of assays for IGF-1 may explain, at least in part, the conflicting results previously reported in diabetic cats. Disorders such as hyperthyroidism and lymphoma affected IGF-1 concentrations, making interpretation of results more difficult if these conditions are present in cats with diabetes.

*J. Intern. Med. 2012; 272: 597-604*

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## Geographical differences



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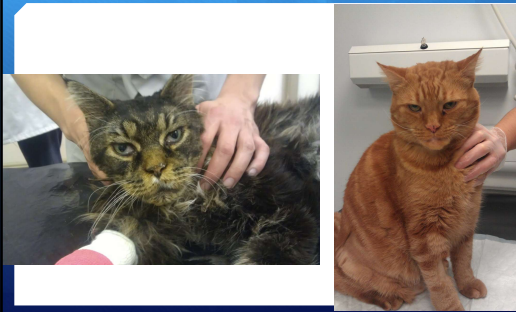
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## Prevalence

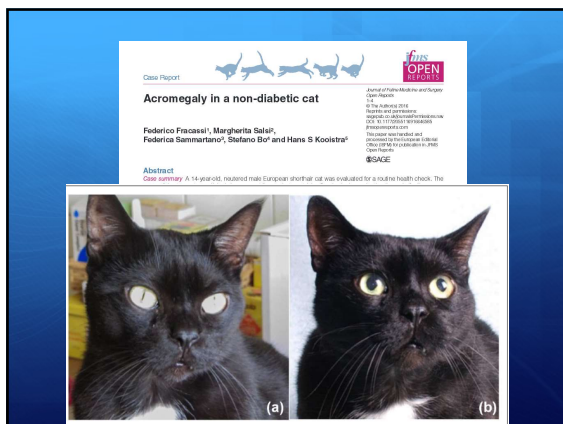
- + Exact prevalence remains unknown
- + But the message is the same:
- + Acromegaly is still a common cause of DM in cats

22

## Boots (2007)

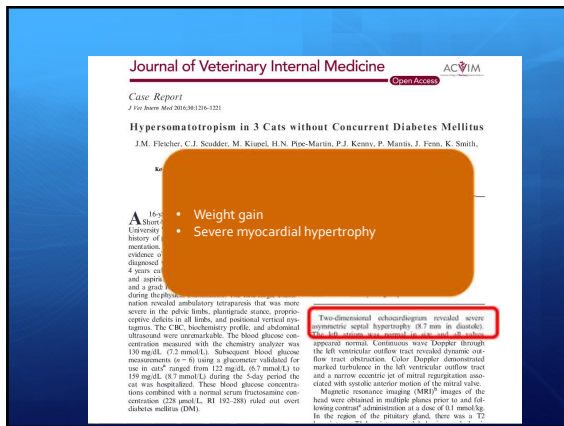


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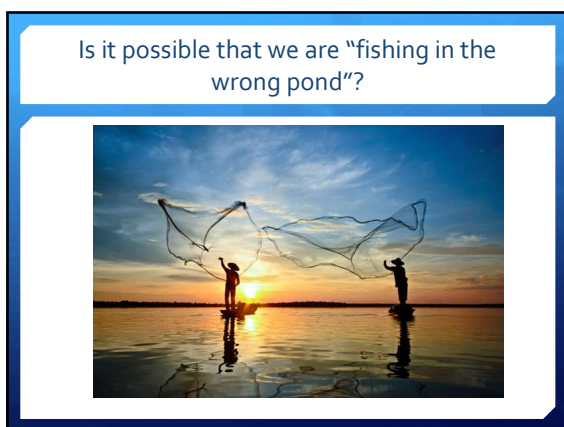




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27

## Acromegaly in human medicine

- + 2004: American Association of Clinical Endocrinologists – acromegaly “rarely diagnosed disease”
  - + Estimated anual incidence 3-4 casos/ million
- + 2011 recommendations were changed:
  - + New studies suggest higher incidence
  - + Belgium: 130 / million
  - + Germany: 1,034 / million
  - + Reasons: adjusting diagnostic criteria and higher awareness/knowledge about the disease
- + “Most acromegalic patients are not diagnosed early on”

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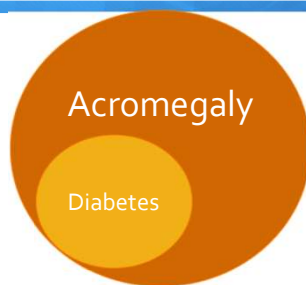
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## Feline acromegaly



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## Prevalence in non-diabetics

D.J. Connolly; J.R. Payne; K. Borgeat; D.B. Church; M. Steele; P. Coss; S.J.M. Niessen.  
**Prevalence of Hypersomatotropism in Non-Diabetic Cats with Left Ventricular Hypertrophy - A Silent and Curable Phenocopy for Hypertrophic Cardiomyopathy**  
 28th ECVIM-CA Congress, 2018

- N= 66 cats
- Diagnosed with HCM
- 6% IGF-1 >100ng/ml

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Can we use the phenotype?

➤ **Most extensive case series** Niessen 2011

- + N=323 cats suspected of having acromegaly
- + Mostly male neutered (70%)
- + Mean age: 11.3 +/- 2.7 years (range: 4-19)
- + Mostly (87%), Maine Coon (2%)
- + Very similar to the average diabetic population
- + Differences:
  - + Weight
  - + Fructosamine
  - + Average insulin dose: 15 iu/day vs 6 iu/day

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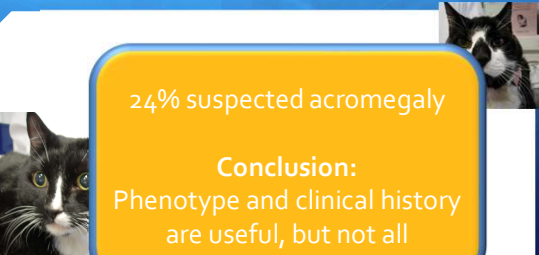
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>300 veterinarians sent samples

24% suspected acromegaly

**Conclusion:**  
Phenotype and clinical history  
are useful, but not all



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Can we trust IGF-1?

- + Problems
  - + false + in diabetics
  - + false – in newly diagnosed diabetics
  - + Differences in methodology
- + It is a good test in general
  - + 94% specificity if > 1000 ng/ml Niessen et al. 2013

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Can we trust IGF-1?



	Fruct	Insulin	BW	IGF-1
Month o	680	1	3.95	212

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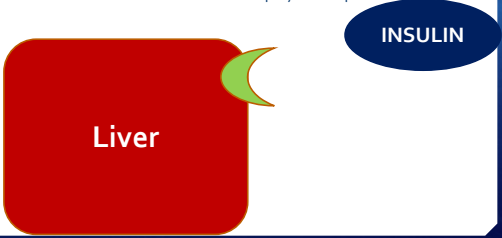
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False negative in newly diagnosed diabetics?

- + Why?
- + Duration of insulin administration plays an important role



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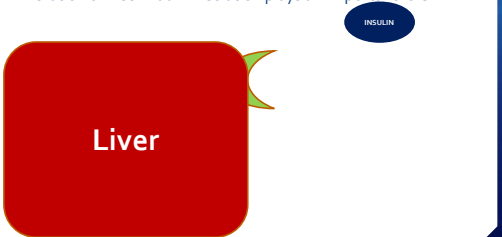
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False negative in newly diagnosed diabetics?

- + Why?
- + Duration of insulin administration plays an important role



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Falso negativo en nuevos diabéticos?

- + Nuevos diabéticos (<6semanas desde el diagnóstico)
- + Múltiple IGF-1s
- + N=413

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### Can we trust IGF-1?

- + Sensitivity 90% & specificity 94-95% at 1000 ng/ml

Best available diagnostic test  
Careful in newly diagnosed diabetics  
Careful in choice of lab

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### GH and Glucose GH suppression test

- + GH
  - + Pulsatile secretion (less reliable?)
  - + No acromegalic cat had a normal GH on a previous study  
Niessen et al 2007a/b
- + Glucose infusion reduces pulsatile secretion of basal GH secretion
  - + Little evidence in cats
  - + 1 paper describes this in acromegalic cats (Eigenmann et al., 1984)
  - + No suppression in 4 healthy cats (Kokka et al., 1971)

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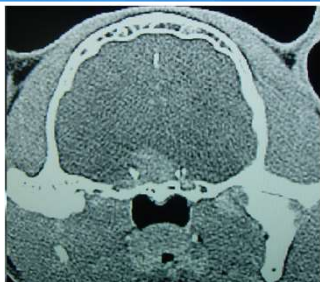
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### Diagnostic imaging



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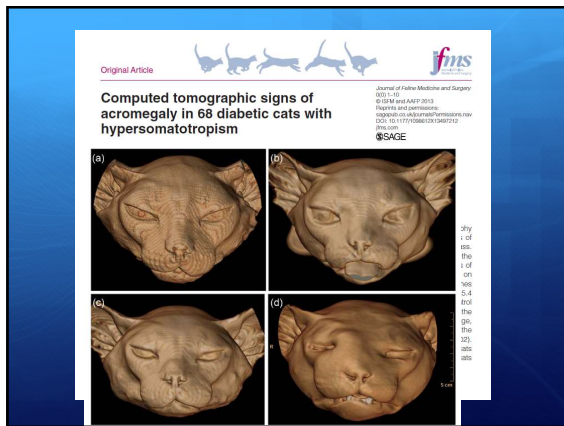
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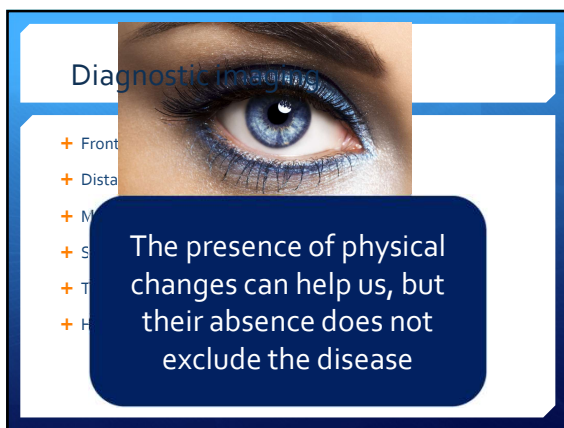
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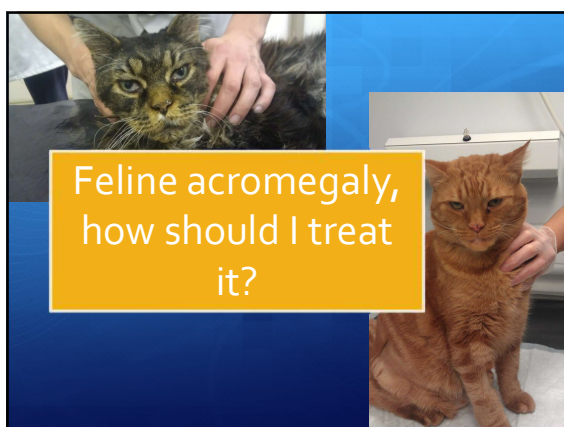
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### Non-invasive treatment

Conservative:

- + Insulin
  - + Unlikely to achieve good glycemic control
  - + Risk hypoglycemia
  - + Quality of life is important
- + Treatment of additional signs
  - + Polyphagia (Fluoxetine)
  - + HCM
  - + Arthritis, etc.



46

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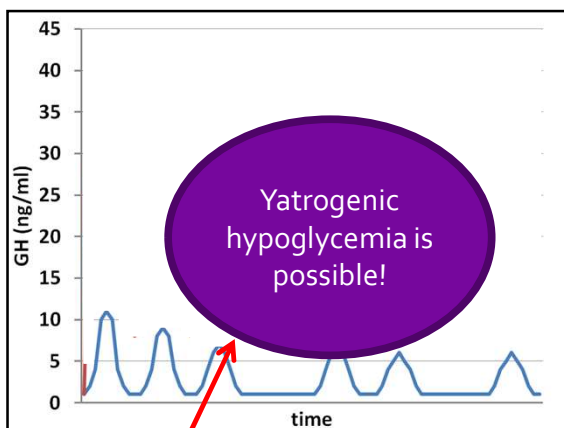
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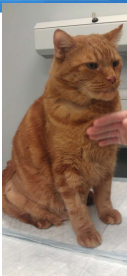
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### Non-invasive: Pasireotide

- + SOM230 (Signifor®, Novartis, Basel, Switzerland)
  - + Non-specific somatostatin analogue
  - + High affinity somatostatin receptors 1, 2, 3 & 5
  - + Suppresses GH, IGF-1 & ACTH in mice and humans with acromegaly



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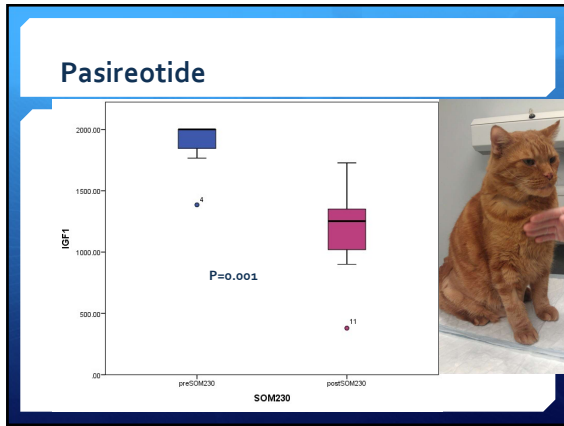
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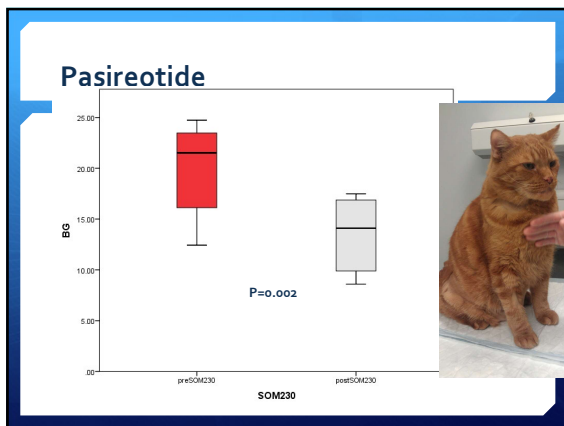
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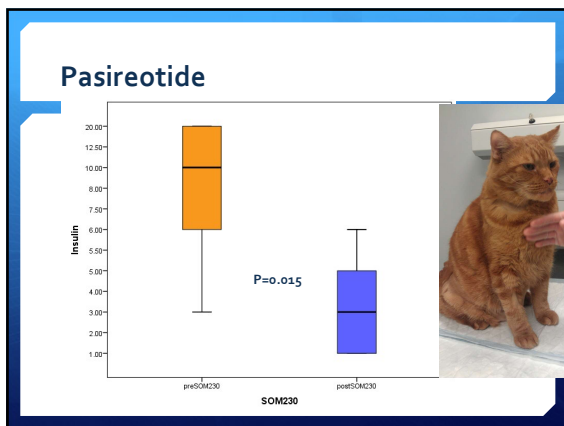
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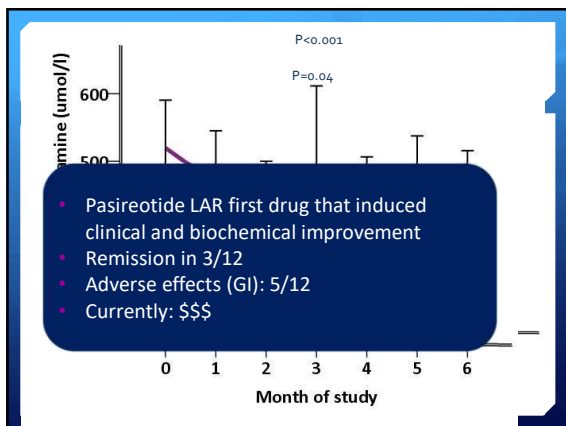
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52

**Pharmacological treatment with cabergoline in three cats with acromegaly<sup>a</sup>**

**Tratamiento farmacológico con cabergolina en tres gatos con acromegalia**

**Tratamiento farmacológico con cabergolina en tres gatos con acromegalia**

Elbert A Seler Arias<sup>a</sup>, MV; Sp; Jorge D García, MV; Victor A Castillo, MV

<sup>a</sup>Unidad de Endocrinología, Área de Clínica Médica de Pequeños Animales, Hospital Escuela, Facultad de Ciencias Veterinarias, Ciudad Autónoma de Buenos Aires, Argentina

(Received: November 10, 2016; accepted: April 22, 2017)

doi: 10.17533/udavet.v5i0a0607

**Abstract**

**Anamnesis:** Three cats diagnosed with diabetes mellitus (DM) were referred for examination due to the presence of insulin resistance signs, which included polyuria, polydipsia, polyphagia and high fructosamine levels, even with insulin glargine doses greater than 2 U/kg application. **Clinical and laboratory findings:** All patients had enlarged facial features along with increased interdental spaces. The biochemical tests revealed high IGF-1 concentrations. The magnetic resonance imaging displayed enlarged pituitary gland in one of the cats and images compatible with a pituitary macroadenoma in the other two. Acromegaly was the final diagnosis. **Treatment approach:** Oral cabergoline at 10 µg/Kg every 48 h was administered. **Conclusion:** The treatment with cabergoline successfully decreased IGF-1 concentrations and all insulin resistance signs, and it enhanced glycemic control for the DM in the three cats. Our results suggest cabergoline could be used for the treatment of acromegaly in cats.

**Keywords:** diabetes, dopaminergic agonist, growth hormone, hypersecretorism, IGF-1, insulin resistance.

53

**Invasive treatment: radioterapy**

- + Reduces size of adenoma
- + Improves diabetic control
- + Few complications

6 months

PRE-radiation POST

54

### Invasive treatment: Radiation

- + Takes some time to work
- + Difficult to predict how long
- + Requires anesthesia
- + Improves DM but does not reduce IGF-1
  - + HCM persists
  - + Other disease features progress

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### Hypophysectomy

- + Probably best treatment option
- + Removes the tumour
- + GH concentration normalises within hours
- + High chance of remission

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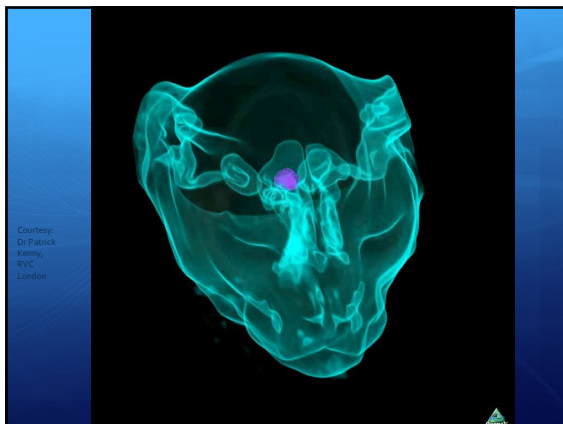
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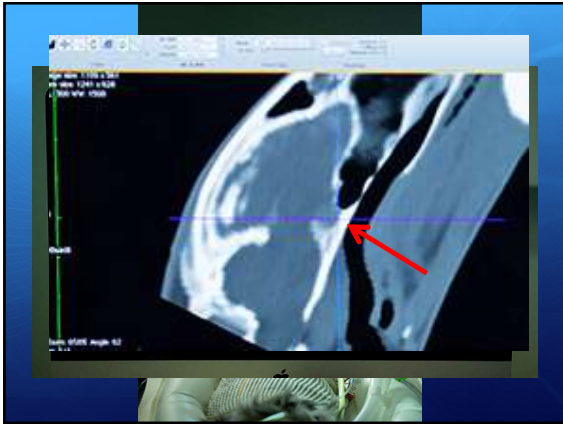
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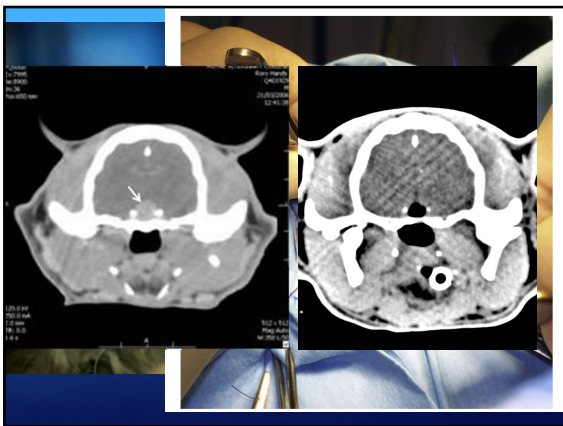
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### Hypophysectomy

- + Post-surgical period:
  - + Hydrocortisone q24h
  - + Thyroid hormone q24h
  - + First three weeks: DDAVP drops q 8h
  - + 20%: DDAVP a long term
    - + Q8-24h
- + Insulin requirements go down progressively

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Conclusions

- + Acromegaly is common in diabetic cats
- + Starting to see it in non-diabetic cats
- + Clinical signs can be subtle
- + Important to be aware of diagnostic tools and their limitations
  - + IGF-1
  - + False negatives in newly diagnosed cats

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