

## Can Iodine-restricted Diets Normalise Serum Total Thyroxine (TT4) and Subsequently Improve Clinical Signs in Cats With Hyperthyroidism?

A Knowledge Summary by

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ISSN: 2396-9776

Published: 19 Feb 2019

in: Vol 4, Issue 1

DOI: <http://dx.doi.org/10.18849/ve.v4i1.176>

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Next Review Date: 19 Feb 2021

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## PICO question

In cats with hyperthyroidism, does an iodine-restricted diet normalise the serum TT4 (total thyroxine) levels and reduce the severity of the clinical signs when compared to cats on a normal diet?

## Clinical bottom line

Whilst there is some evidence that iodine-restricted diets can help to renormalise serum TT4 in cats with hyperthyroidism, this is not always effective and there is a lack of compelling evidence to suggest this is associated with a resolution of clinical signs in the long-term.

## Clinical Scenario

Often, a diagnosis of feline hyperthyroidism raises more questions than it solves; with owners striving for a noninvasive and simple treatment for their usually geriatric cat. For the clinician, this has traditionally involved a choice between surgery, lifelong medical management or radioactive iodine treatment. Surgery is invasive, irreversible and carries the risks of anaesthetising a geriatric patient with a strong possibility of concurrent disease. Whereas traditional medical management is lacking in options, often resulting in owners being left with the task of daily/twice-daily tableting of a potentially noncompliant cat. This is often difficult for owners to achieve, and radioactive iodine treatment is only available at limited centres, with owners being required to leave their beloved pet for long periods. What if something as simple as a dietary change could help manage the disease?

## Summary of the evidence

Hui et al., (2015)	
<b>Population:</b>	Client-owned cats with hyperthyroidism
<b>Sample size:</b>	49
<b>Intervention details:</b>	Cats with hyperthyroidism were fed solely on an iodine-restricted diet.
<b>Study design:</b>	Retrospective case series
<b>Outcome studied:</b>	Objective assessment of: <ul style="list-style-type: none"> <li>● Heart Rate</li> <li>● Serum TT4</li> <li>● Blood Urea Nitrogen (BUN)</li> <li>● Creatinine</li> </ul> Subjective assessment of: <ul style="list-style-type: none"> <li>● Weight – Body Condition Score (BCS)</li> </ul>
<b>Main findings: (relevant to PICO question):</b>	<ul style="list-style-type: none"> <li>● Serum TT4 was normalised in 83% of cats by 180 days.</li> <li>● Normalisation of TT4 did not lead to any improvement of</li> </ul>

	<p>weight or heart rate.</p> <ul style="list-style-type: none"> <li>• However, weights did stabilise and clinical signs did not worsen.</li> </ul>
<b>Limitations:</b>	<ul style="list-style-type: none"> <li>• Retrospective case studies are relatively low down the evidence hierarchy.</li> <li>• Multiple laboratories used for blood analysis.</li> <li>• Serum TT4 and physical parameters were monitored only for a limited time period of 8 weeks.</li> <li>• Nine cats had already been treated using methimazole.</li> </ul>

<b>van der Kooij et al., (2014)</b>	
<b>Population:</b>	<p>Group 1: Hyperthyroid cats previously medicated with antithyroid medications.</p> <p>Group 2: Recently diagnosed and untreated hyperthyroid cats.</p>
<b>Sample size:</b>	225
<b>Intervention details:</b>	Hyperthyroid cats were fed solely on an iodine-restricted diet.
<b>Study design:</b>	Prospective, multi-centre study.
<b>Outcome studied:</b>	<p>Subjective assessment:</p> <ul style="list-style-type: none"> <li>• Body condition score (1–5)</li> <li>• Clinical signs were scored by owners and vets at day 0, week 4 and week 8.</li> </ul> <p>Objective assessment:</p> <ul style="list-style-type: none"> <li>• TT4</li> <li>• Urea</li> <li>• Creatinine</li> </ul>
<b>Main findings: (relevant to PICO question):</b>	<ul style="list-style-type: none"> <li>• Serum TT4 was normalised in 75% of cats by 56 days.</li> <li>• In the remaining 25%, serum TT4 was lower but still above the reference range.</li> <li>• Clinical signs were perceived to have improved by both the owners and veterinarians.</li> <li>• BCS stabilised during the course of the study.</li> </ul>
<b>Limitations:</b>	<ul style="list-style-type: none"> <li>• Weight was monitored with subjective body condition scores, rather than using scales, and by multiple different assessors.</li> <li>• Multiple laboratories were used, with different reference ranges.</li> <li>• Missing data due to voluntary participants.</li> <li>• Not documented if wet or dry food was used – the two contain differing levels of iodine.</li> </ul>

<b>Fritsch et al., (2014)</b>	
<b>Population:</b>	Client-owned cats over 10-years-old, with suspected hyperthyroidism and with a serum TT4 > 4.0 ug/dL
<b>Sample size:</b>	22 cats completed the study.
<b>Intervention details:</b>	12 cats were fed a prototype restricted iodine diet and ten were fed a control diet.

<b>Study design:</b>	Randomised control trial.
<b>Outcome studied:</b>	Cats were assessed at 0, 3, 6 and 12 weeks. Subjective assessment: <ul style="list-style-type: none"> <li>• Physical examination</li> </ul> Objective assessment: <ul style="list-style-type: none"> <li>• Urine specific gravity</li> <li>• TT4, FT4 and T3</li> <li>• BUN</li> <li>• Creatinine</li> <li>• Alkaline phosphatase (ALP), alanine transaminase (ALT) and aspartate aminotransferase (AST)</li> </ul>
<b>Main findings: (relevant to PICO question):</b>	<ul style="list-style-type: none"> <li>• All cats fed the iodine-restricted diet had decreased TT4 concentrations by the end of the study, with half attaining euthyroid status.</li> <li>• In the control group, TT4 was increased in four cats, was reduced in four cats and stable in two.</li> <li>• No cats in the control group achieved euthyroid status.</li> <li>• Serum creatinine, BUN, AST, ALT and urine specific gravity (USG) remained stable or decreased in cats fed the iodine-restricted diet.</li> </ul>
<b>Limitations:</b>	<ul style="list-style-type: none"> <li>• Funded and designed by Hill's Pet Nutrition, producer of the iodine-restricted diet.</li> <li>• Relatively small sample sizes.</li> <li>• Whether or not there was a resolution of clinical signs was not mentioned in the discussion.</li> </ul>

<b>Vaske et al., (2016)</b>	
<b>Population:</b>	Client-owned cats with hyperthyroidism.
<b>Sample size:</b>	15
<b>Intervention details:</b>	Cats were fed an iodine-restricted diet (Hills y/d, the proprietary diet produced by Hill's Pet Nutrition) dry or canned version) and assessed at 0, 1, 2, 3 & 6 months
<b>Study design:</b>	Prospective study
<b>Outcome studied:</b>	Subjective: <ul style="list-style-type: none"> <li>• Physical examination</li> </ul> Objective: <ul style="list-style-type: none"> <li>• TT4</li> <li>• Haematology</li> <li>• Biochemistry</li> <li>• Symmetric dimethylarginine assay (SDMA)</li> <li>• Urinalysis, urine protein to creatinine ratio (UPC), gamma-glutamyl transferase (GGT) and creatinine</li> <li>• Systolic BP</li> </ul>
<b>Main findings: (relevant to PICO question):</b>	<ul style="list-style-type: none"> <li>• TT4 was reduced in 100% of the cats after 6 months.</li> <li>• 9–10 cats remained persistently hyperthyroid after 6</li> </ul>

	months.
<b>Limitations:</b>	<ul style="list-style-type: none"> <li>• Funded and designed by Hill's Pet Nutrition, producer of the iodine-restricted diet.</li> <li>• Very small sample size.</li> <li>• Whether or not there was a resolution of clinical signs was not mentioned in the discussion.</li> </ul>

Scott-Moncrieff (2015)	
<b>Population:</b>	Client-owned hyperthyroid cats.
<b>Sample size:</b>	8
<b>Intervention details:</b>	Cats were fed an iodine-restricted diet for 6 months.
<b>Study design:</b>	Prospective study
<b>Outcome studied:</b>	Subjective: <ul style="list-style-type: none"> <li>• Physical examination</li> </ul> Objective: <ul style="list-style-type: none"> <li>• TT4</li> <li>• fT4</li> <li>• Haematology</li> <li>• Biochemistry</li> <li>• Urinalysis</li> <li>• <sup>123</sup>I (a radioactive Iodine isotope) uptake by thyroid glands scintigraphically</li> </ul>
<b>Main findings: (relevant to PICO question):</b>	<ul style="list-style-type: none"> <li>• Clinical signs reportedly resolved.</li> <li>• Both TT4 and fT4 were significantly improved, with 7/8 cats achieving euthyroid status by week 8.</li> <li>• No significant change in body weight.</li> </ul>
<b>Limitations:</b>	<ul style="list-style-type: none"> <li>• Very small sample size.</li> <li>• Whilst it is stated that clinical signs resolved, there is no standardised assessment described.</li> </ul>

## Appraisal, application and reflection

During the literature search, it soon became apparent that there were only limited studies investigating the efficacy of the relatively recently introduced iodine-restricted diets for successful control of feline hyperthyroidism. A second point of note was that a substantial proportion of the studies into iodine-restricted diets were undertaken in conjunction with Hill's Pet Nutrition, a key developer and producer of the commercially available diet, and unfortunately this introduces a suspicion of potential bias in those studies. Both the papers from van der Kooij et al., (2014) and Hui et al., (2015) used a large sample population, but unfortunately the studies by Fritsch et al., (2014), Scott-Moncrieff et al., (2015) and Vaske et al., (2016) had more limited sample sizes of 22, 8 and 15 respectively, reducing the reliability of their findings. A limitation of all the studies into this subject is the difficulty in maintaining and proving 100% compliance, as all the patients enrolled in the studies were client-owned and potentially allowed outdoor access. As well as this, documenting an improvement in clinical signs is difficult, given the subjective nature of the task, and made more complicated by the fact that the cats were only assessed by veterinarians at set intervals (it is also unclear whether or not these assessments were made by the same veterinarian). van der Kooij et al., (2014) used an online questionnaire, allowing owners to submit data regarding the clinical signs, however

details of the questionnaire are not included in the paper, so its suitability cannot be assessed. Finally, the limited follow-up undertaken during any of the studies reduces the value of any conclusions that can be made.

Hui et al., (2015) included nine cats which had already been taking methimazole as treatment, prior to starting the iodine-restricted diet. Whilst it was ensured methimazole treatment had been halted, and TT4 was over the reference range before starting the iodine-restricted diet and including these cats in the study, there was no information regarding how long the methimazole had been stopped for, or whether TT4 had returned to pre-methimazole treatment levels.

All of the studies found that by the end of their follow-up period 100% of the cats had lower serum TT4 values than when they were started on the iodine restricted diet. Hui et al., (2015) found that by 61–180 days into treatment serum TT4 had normalised in 83% of the cats in the study. van der Kooij et al., (2014) had similar findings, with 75% of those cats having normal serum TT4 by week 8. Similarly, Scott-Moncrieff et al., (2015) found serum TT4 normalised in seven out of eight cats by week 8. Fritsch et al., (2014) reported 50% of the enrolled cats becoming euthyroid by week 12 and Vaske et al., (2016) had 33% of the cats become euthyroid by 6 months into treatment.

Neither of the studies by Fritsch et al., (2014) or Vaske et al., (2016) monitored clinical signs during the iodine-restricted diet trial, so it is impossible to draw any conclusions regarding improvement of clinical signs from these studies. Hui et al., (2015) documented a cessation of the progression of clinical signs, whilst both Scott-Moncrieff et al., (2015) and van der Kooij et al., (2014) showed an improvement, perceived by both owners and veterinarians.

No cats were removed from any of the studies due to concerns about the safety of the diet, or as a result of any side effects, so it can be concluded at least that the diet is safe.

So whilst there is limited literature investigating the efficacy of iodine-restricted diets as a treatment for feline hyperthyroidism, all the studies so far have documented a 100% improvement in serum TT4 when cats have been started on an iodine restricted diet, though this did not always guarantee a return to euthyroid status. There is, however, a lack of consensus regarding the resolution of clinical signs. Further to this disparity amongst the literature, the limited number of studies and the limitations of those studies mean a prospective study with large sample size and– lifelong follow-up would improve the evidence base greatly.

## Methodology Section

Search Strategy	
Databases searched and dates covered:	OVID Medline on OVID SP 1946 – Week 4 2019 Web of Science Core Collection on Web of Science 1946 – Week 4 2019 OVID CAB Abstracts 1973 – Week 4 2019
Search terms:	'Animal Feed' OR 'Diet' AND 'Cats' OR 'Feline' AND 'Hyperthyroidism'
Dates searches performed:	22/01/19

Exclusion / Inclusion Criteria	
Exclusion:	Articles not in English, unrelated to the PICO, single case reports, book chapters and conference proceedings.
Inclusion:	Articles in English, related to the PICO.

Search Outcome					
Database	Number of results	Excluded – Relevance	Excluded – Language	Excluded – Duplicates	Total relevant papers
Ovid Medline	228	225	0	0	3
CAB Abstracts	485	480	0	3	2
Web of Science	24	19	0	5	0
Total relevant papers when duplicates removed					5

## CONFLICT OF INTEREST

The author declares no conflicts of interest.

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