Title

Prevalence of canine primary hyperparathyroidism recurrence in Keeshond and non-Keeshond dogs having undergone curative parathyroidectomy

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ABSTRACT

Background

Primary hyperparathyroidism (PHPT) is an uncommon condition in dogs, for which there is a documented genetic predisposition in Keeshonden and sporadic cases in other breeds. Secondary literature reports a 10% prevalence for recurrence in patients successfully treated by surgical parathyroidectomy, however there is no published primary literature available on which to base this assertion. This study sought to document prevalence of recurrence within Keeshonden and non-Keeshonden breeds. The authors hypothesised that Keeshonden would have a higher rate of recurrence due to the genetic predisposition for the disease, as compared to sporadic cases in other breeds, and that Keeshonden might have an earlier age of detection of disease.

Methods

A retrospective review of medical records was undertaken to assess the prevalence of recurrence, the length of time after diagnosis that the recurrence occurred, and the age of initial diagnosis in both Keeshonden and non-Keeshonden breeds.

Results

The study found that Keeshonden were significantly more likely to develop recurrence (6/12, 50%) than non-Keeshond dogs (1/15, 7%), (p=0.024), and were significantly younger (median 108 months vs 126 months, p=0.043) at initial disease detection. Recurrence in Keeshonden occurred at median 35 months after treatment.

Conclusion

This suggests all dogs treated by curative parathyroidectomy for PHPT should be monitored lifelong for recurrence of disease, and that this is particularly pertinent in the Keeshond population. Earlier screening of younger, apparently healthy Keeshonden may also be advisable.
Introduction

Canine primary hyperparathyroidism (PHPT) is a relatively uncommon condition whereby one or more of the parathyroid glands begins producing parathyroid hormone (PTH) autonomously. This leads to excessive bone resorption, increased absorption of calcium within the gastrointestinal tract and increased renal tubular reabsorption of calcium, resulting in a state of total and ionised hypercalcaemia. Diagnosis of the disease is made by documentation of inappropriately increased (within or above the normal reference range) PTH in the face of total and ionised hypercalcemia. Previous literature has suggested that roughly 87% of cases of canine PHPT are the result of a benign parathyroid adenoma, 8% are due to hyperplasia of the parathyroid gland(s) and only 5% result from parathyroid carcinoma. However, there is also acknowledged difficulty in differentiating the histopathologic appearance of adenoma and hyperplasia, and limited clinical benefit in designating the pathology as one or other with regard to treatment or prognosis. Amongst the population of dogs with PHPT, >90% have disease confined to a single parathyroid gland at the time of diagnosis. A single reference (Feldman 2015) within the veterinary literature suggests that roughly 10% of cases in all breeds treated for PHPT will develop recurrence of the disease, however there is no primary literature currently available to support this. A further single case of recurrence >6 months after curative surgical treatment is documented in a PTH assay validation study, however due to the nature of the study there are limited case details provided.

Hyperparathyroidism is also encountered in human medicine, where multiple genes have been linked to the development of PHPT either as a standalone condition (Familial isolated hyperparathyroidism, FIHP) or as part of a number of defined syndromes. Of these syndromic cases, 35% are associated with multiple endocrine neoplasia 1 (MEN1) mutations, with smaller numbers associated with multiple endocrine neoplasia 2 (MEN2A), calcium-sensing receptor (CaSR, causing both FIHP and familial hypocalciuric hypercalcaemia [FHH]) and CDC73 (causing hyperparathyroidism-jaw tumor, HPT-JT), amongst numerous other further-rarer mutations.
Studies in human medicine initially identified a recurrence rate across all cases of 4% within five years after initial curative surgical treatment, however this analysis was performed on a mixed, non-genotyped population. A more recent study of a genotyped population looked at patients with known genetic mutations vs those without. Notably, this identified a 0% incidence of recurrence within the 68 patients that did not carry MEN1, MEN2A or CaSR mutations. Assessment of the mutation carrying patients, however, found that 14 out of the 29 cases where one or more mutation was detected developed recurrence of PHPT after a mean of 7±5 years. More recently, three further candidate genes have been identified that reportedly cause FIHP and FHH. A further report on FIHP in 2019 identified a mutation of the gene for the GCM2 transcription factor in 17% of patients. Typically, these patients with FIHP and the GCM2 germline activating mutation present as adults with multiple parathyroid tumours. Mutations in GNA11, a G-protein required for the functioning of the calcium sensing receptor, have been found to cause FHH type 2 in people whilst AP2S1 is mutated in the human population with FHH type.

By comparison, the canine population is viewed as being homogenous, with one diagnosis, that of primary hyperparathyroidism, being made across all breeds. Whether this is a true reflection of the aetiopathogenesis of canine parathyroid-mediated hypercalcaemia is not clear but, given the breadth of diagnoses in human medicine, it is likely to be an oversimplification. Within the canine PHPT population, the majority of dogs are considered to develop non-genetically predisposed disease. However, there is also an autosomal dominant inherited breed predisposition amongst Keeshonden, with one study reporting the odds ratio for this breed at 50. Considerable work has been performed by way of a candidate gene approach assessing for association with mutations in the MEN1, HRPT2 and CaSR genes in Keeshonden, however this failed to implicate a specific causal mutation. For temporal reasons, the recently identified GCM2, GNA11 and AP2S1 mutations were not included in this work. A genome-wide search for the gene responsible for canine PHPT was carried out and this work led directly to the development of a genetic test for Keeshonden.
that is run by the Animal Health Diagnostic Centre at Cornell University\textsuperscript{17}. This commercial genetic test identifies the mutation or a closely linked polymorphism, and is available for owners and breeders prior for screening and to inform mating decisions. The test appears to be able to differentiate between normal dogs and dogs likely to develop PHPT but the molecular mechanism behind the development of the disease has not been proven and the work remains unpublished.

Data on sensitivity, specificity and predictive values are not freely available for this genetic test.

The purpose of this study is to document the overall prevalence of recurrence of PHPT within the PHPT-affected canine population, and to assess both the Keeshond and non-Keeshond population for recurrence following parathyroidectomy. We hypothesise that the prevalence of recurrence will be higher in the Keeshond population as a result of the known familial allelic mutation when compared to the prevalence in cases in other breeds.

Materials and Methods

Ethical approval for this study was granted by the Department of Veterinary Medicine, University of Cambridge Ethics Committee.

The records of the Queen’s Veterinary School Hospital, Cambridge, UK were searched for cases of canine primary hyperparathyroidism diagnosed between 2009-2018 in Keeshond and non-Keeshond breeds. Inclusion criteria included total and ionised hypercalcaemia, a documented inappropriately elevated parathyroid level in the face of hypercalcaemia and resolution of the hypercalcemia after parathyroidectomy of the affected glands for at least 6 months. Dogs were excluded if they had comorbidities known to result in hypercalcaemia, had a high PTH-rP or were on medications expected to alter calcium balance at the time of diagnosis or follow-up. Inclusion was permitted for dogs receiving calcium-reducing drugs as part of their pre-operative management after initial PHPT diagnosis, and for dogs requiring calcium and vitamin D supplementation in the immediate post-
operative period. Further recruitment of four cases into the Keeshond group was achieved through contact with the Health Co-ordinator of the UK Keeshond Club.

Data were collected on signalment, total and ionised calcium levels, PTH/PTH-rP, diagnostic imaging findings, number of parathyroid glands removed and development of recurrence. Recurrence was defined as a return to normocalcemia for a minimum of six months after parathyroidectomy followed by redevelopment of hypercalcemia after cessation of any calcium or vitamin D supplementation. This definition was based on previous studies, where development of hypercalcaemia prior to this time was classified as treatment failure.\textsuperscript{5,11} Repeat PTH/PTH-rP measurement and imaging were considered highly desirable but not necessary in the absence of another hypercalcemia-causing disease being identified. This was driven in part by the retrospective nature of the study and in part by the high cost of measurement of these parameters for owners who had made the decision not to pursue further investigation and treatment.

Continuous data were assessed for normality using a Shapiro-Wilk test (SPSS). Prevalences were calculated as a percentage of overall cases and statistical testing was performed using a Fisher’s Exact test and chi squared test with Yates correction (Graphpad). Population comparisons were analysed on the normally distributed data using a students T-test (Excel).

Results

A total of 31 dogs with primary hyperparathyroidism were identified. Four non-Keeshond dogs were subsequently excluded due to their owners electing not to proceed with parathyroidectomy, leaving a study population of 27 dogs (23 from the QVSH, 4 sourced with the help of the UK Keeshond Club) with documented successful surgical treatment of hyperparathyroidism. Of these, 12 dogs were Keeshonden and 15 were non-Keeshond. Breeds represented in the non-Keeshonden group included two each of: Border Terrier, Jack Russell Terrier and Weimaraner; and one each of: Airedale Terrier, Beagle, Bernese Mountain Dog, Crossbreed, Lakeland Terrier, Leonberger, Rhodesian Ridgeback, Shih Tzu and Springer Spaniel. All patients (both groups) successfully treated with surgical
management had documented normal ionised calcium levels post-surgically on between three and five occasions during the six months after surgery (excluding the five-day immediate post-operative period when ionised calcium was measured daily in all cases) as part of standard ongoing monitoring as outpatients. No dogs had a measured hypercalcaemia within this time period.

Within the non-Keeshond group there were nine male and six female dogs, with a median age 126 months at time of diagnosis (range: 60-168). This group had a median total calcium of 3.34 mmol/L (ref: 2.2-2.9), with a mean of 3.49 and standard deviation of 0.35. The ionised calcium median was 1.81 mmol/L (ref: 1.14-1.4), with a mean of 1.84 and standard deviation of 0.21. Parathyroid hormone was measured in all non-Keeshond dogs and was very varied, with a median of 212 pmol/L (ref: 20-65), mean of 275 and standard deviation of 272 and range of 46-1000. (table 1.)

<table>
<thead>
<tr>
<th></th>
<th>Keeshond</th>
<th>Non-Keeshond</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>Mean</td>
<td>98.5</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>19.2</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>108.0</td>
</tr>
<tr>
<td>Total Calcium (mmol/L)</td>
<td>Mean</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>3.5</td>
</tr>
<tr>
<td>Ionised Calcium (mmol/L)</td>
<td>Mean</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>2.1</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>Mean</td>
<td>267.6</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>169.3</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>233.5</td>
</tr>
</tbody>
</table>

Table 1.

Ultrasound examination of the parathyroid glands was undertaken in all non-keeshonds prior to surgery, and in all cases recorded the presence of a single ‘prominent’ or ‘enlarged’ parathyroid gland, with other glands being variably reported as ‘small’, ‘normal’ or ‘not-found’. Absolute sizes of glands were not reliably enough reported in the clinical records of these patients to allow further evaluation.

All dogs underwent a parathyroidectomy of the single gland within which a nodule/enlargement had been identified. Histology on the excised tissues from this group reported the presence of an
adenoma in 14/15 dogs. The remaining case had histology performed but no final decision on whether to describe the findings as adenoma or hyperplasia was reported.

Of the 15 dogs in the non-Keeshond group, one dog developed recurrence (7%). Recurrence in this dog was documented on routine screening 14 months after parathyroidectomy, at which time an ionised calcium of 1.61 mmol/L (ref: 1.14-1.4) was documented and a repeat PTH measurement returned a value of 125 pmol/L (ref: 20-65). Two further ionised calcium measurements were taken after recurrence was documented, with ionised calcium remaining above the laboratory specific reference interval on both occasions. None of the remaining dogs had documented hypercalcaemia at any time, with follow-up time ranging from 7-48 months and with serial measurements made at 6-12 monthly intervals in all dogs after treatment success was confirmed. Further cervical ultrasound studies were not performed in any non-keeshond dogs due to the absence of hypercalcaemia (14/15) or lack of will to do so by the owner (in the case of the dog with recurrence), however the dog with recurrence had further abdominal and thoracic imaging to confirm the absence of other hypercalcaemia-causing pathologies.

In the Keeshond group there were seven male and five female dogs, with a median age of 108 months at time of diagnosis (range: 63-120). This group had a median total calcium of 3.54 mmol/L (ref: 2.2-2.9) with a mean of 3.58 and standard deviation of 0.37. The ionised calcium median was 2.07 mmol/L (ref: 1.14-1.4), with a mean of 1.98 and standard deviation of 0.19. Parathyroid hormone was measured in all Keeshond dogs and had a median value of 236 pg/ml (ref: 20-65), mean 296 and standard deviation 155. Cervical ultrasound examination was performed in all Keeshond dogs at the time of initial diagnosis and identified a single enlarged gland in 11/12 cases. In the remaining 1/12 cases, no definitely enlarged gland could be identified by this means. Available clinical records do not report the absolute size of the parathyroid glands sufficiently frequently to allow analysis of affected parathyroid gland size. Non-enlarged glands were reported in all cases either as ‘small’, ‘normal’ or ‘not-found’. All but one dog had a single parathyroid nodule excised, with the remaining dog (that which had no detectable enlarged gland on ultrasound) having three of
four removed. Of these patients, 10/12 were described as adenomas, 1/12 as hyperplasia with the remaining report unavailable. In the post-surgical period, all Keeshonden had ionised calcium measured daily until discharge from the hospital. After this time, ionised calcium was monitored at a maximum of four-weekly intervals until six months post-surgically, during which period all dogs remained normocalcaemic confirming treatment success. After this time, monitoring interval was extended to 6-12 monthly until such time as they recurred or died (table 2).

Within the Keeshond group, six out of the 12 dogs developed recurrence (50%). Recurrence occurred at a mean of 41 months after initial surgery. The clinical data from the recurrent disease documented in Keeshonden is presented in Table 2. All dogs ultimately diagnosed with recurrence were measurably hypercalcaemic on between 2 and 4 separate occasions for confirmation, cervical ultrasound was performed in four of six, and further surgery to resolve the recurrence performed in three of six.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at 1&lt;sup&gt;st&lt;/sup&gt; diagnosis (years)</th>
<th>Ca (mmol/L)</th>
<th>iCa (mmol/L)</th>
<th>PTH (pg/ml)</th>
<th>L or R parathyroid removed</th>
<th>Ca dropped within 24 hrs</th>
<th>Time interval (months)</th>
<th>Age at 2&lt;sup&gt;nd&lt;/sup&gt; diagnosis (years)</th>
<th>Ca (mmol/L)</th>
<th>iCa (mmol/L)</th>
<th>PTH (pg/ml)</th>
<th>Imaging performed to confirm recurrence?</th>
<th>Second gland removed?</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>3.5</td>
<td>N/A</td>
<td>180</td>
<td>Left</td>
<td>Yes</td>
<td>24</td>
<td>12</td>
<td>3.5</td>
<td>1.85</td>
<td>155</td>
<td>Yes</td>
<td>Yes</td>
<td>Required vit D and Ca for rest of life. PTS 1 yr later</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>3.26</td>
<td>N/A</td>
<td>299</td>
<td>Right</td>
<td>Yes</td>
<td>19</td>
<td>10</td>
<td>3.28</td>
<td>N/A</td>
<td>206</td>
<td>Yes</td>
<td>Yes</td>
<td>PTS for orthopaedic pain &gt;2yrs post sec surgery</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>3.29</td>
<td>1.82</td>
<td>100</td>
<td>Three of four glands removed</td>
<td>Yes</td>
<td>7</td>
<td>11</td>
<td>3.55</td>
<td>1.96</td>
<td>362</td>
<td>No</td>
<td>No</td>
<td>Alendronate. Euthanasia for unrelated neoplastic disease</td>
</tr>
<tr>
<td>4*</td>
<td>10</td>
<td>4.27</td>
<td>2.22</td>
<td>492</td>
<td>Right</td>
<td>Yes</td>
<td>37</td>
<td>13</td>
<td>3.38</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
<td>Euthanized due to collapse 2 months hypercalcaemia documented</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>3.82</td>
<td>N/A</td>
<td>N/A</td>
<td>Left</td>
<td>Yes</td>
<td>24</td>
<td>9</td>
<td>3.49</td>
<td>N/A</td>
<td>N/A</td>
<td>Yes</td>
<td>Yes</td>
<td>Euthanasia 4 yrs after 2&lt;sup&gt;nd&lt;/sup&gt; surgery</td>
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<tr>
<td>6**</td>
<td>6</td>
<td>3.15</td>
<td>1.86</td>
<td></td>
<td>Right</td>
<td>Yes</td>
<td>54</td>
<td>10</td>
<td>3.48</td>
<td>N/A</td>
<td>N/A</td>
<td>Yes</td>
<td>No</td>
<td>Dog still alive and clinically well, rising hypercalcaemia</td>
</tr>
</tbody>
</table>

Table 2: Clinicopathological data from the 6 Keeshonden that presented with recurrence of primary hyperparathyroidism. Data is missing either because the test was not run or the results were not retrievable.

*This dog was tested positive for PHPT using the Cornell test when 2 years of age
This dog’s sire was positive for PHPT and had two surgeries in his lifetime, one at age 6 and one at age 11, with a second parathyroidectomy performed at age 12. Further clinical details were not available for this case.
No significant difference was found between the groups with respect to sex, total calcium, ionised calcium or PTH measurements at the time of diagnosis. Keeshonden were found to be significantly younger (108 months) than non-Keeshonden dogs (126 months) at the time of diagnosis (p=0.043) (figure 1.). A Fisher’s exact test and Chi squared with Yates correction were performed to compare the respective prevalences of recurrence. In both tests the difference was found to be significant, with the Fisher’s exact test returning p=0.024 and the chi squared returning p=0.035.

Discussion

In this study there was a significant difference found between the rate of recurrence in Keeshonden (50%) and non-Keeshond dogs (7%), with the rate found to be substantially and significantly higher in Keeshonden (P=0.024). This may be due to a number of reasons. It is possible that it is simply a result of the earlier average age at initial diagnosis (108 vs 122 months in this study), as earlier diagnosis and treatment will likely result in a longer post-treatment lifespan. This presents any individual dog with a longer period of time during which a further parathyroid adenoma or hyperplasia can develop by random chance or by genetic predisposition, and thus increases the likelihood that it might occur. Keeshonden would typically be identified as hypercalcaemic earlier than other breeds and this may be due to the fact that keeshond owners are educated about the disease by their breed health representatives and veterinarians.

It is likely that the increased rate of recurrence of de novo disease in Keeshonden is due to the underlying genetic predisposition for disease development identified using the genetic test offered by the Animal Health Diagnostic Centre at Cornell University. This would be supported by the similar recurrence rates found in human populations with well-characterised genetic predispositions (14/29; 48%) and in keeshonden in this study (50%). Although the precise mutation and therefore
the molecular pathway by which this mutation has its effect remain unknown, there are multiple possible means by which it may result in PHPT.

One possibility is that the mutation results in an alteration of the physiologic calcium set-point. An increase in the set point would result in increased drive for PTH production to maintain the higher serum calcium concentration, and this sustained drive to produce the hormone may conceivably lead to development of hyperplasia or adenoma formation. After the higher set point level was reached by the hyperplastic or adenomatous gland, an intact negative feedback loop (as would be anticipated) would be expected to inhibit production of PTH by the remaining glands, neutralising the drive for further hyperplasia and adenoma formation in other glands, and meaning it would be most likely that a single enlarged parathyroid gland be found during investigation in these patients.

Once the offending parathyroid gland(s) was removed the calcium would be expected to return quickly to lower levels, however once the suppression of the remaining glands was resolved the inherent higher set-point would be expected to drive further hyperplasia of one or more of the remaining glands, leading to recurrence of the disease over time. It is of note that the same physiologic pressures would be exerted on both the remaining parathyroid glands and also on any ectopic tissue present outside of the normal parathyroid locations.

However, this hypothesis alone does not address why only one gland of the four generally responds to the increased calcium set-point initially and then, why further glands respond generally one at a time subsequent to parathyroidectomy. For this to be the case, a mechanism causing transformation to an adenoma, resulting either from the overactivity of the parathyroid secreting chief cells or from the genetic mutation, would also be required. Without this, and therefore the development of an adenoma that can provide PTH and calcium-mediated suppression of the other glands, hyperplasia of all four parathyroid glands would be expected to be encountered equally. Although the calcium set-point hypothesis suggests that all four glands may respond to the pressure to raise the serum calcium concentration, evidence from human literature for many of the syndromes discussed earlier, including FIHP and FHH, suggests that in the cases where there is hyperplasia or adenoma
development, frequently one gland only responds. The parathyroid response to some genotypes, particularly of FHH, is that mild-to-moderate over-production of PTH occurs but hyperplasia and adenomas are not identified. Thus the gross and histopathological findings are variable and aligned with genotype. 18.

Alternatively, the mutation may cause an absolute increase in the likelihood of adenoma development in any individual gland as a result of increased nuclear protein expression within the parathyroid cells. Although suppression of other parathyroid glands by a functional adenoma may result in reduced likelihood of further adenoma development in other glands, it might be expected that an absolute increase in likelihood may result in a higher frequency of dogs developing hyperplasia or adenomas in two or more glands contemporaneously. This is not supported by the findings in this study although has been previously reported6.

One dog in the Keeshond group had three out of the four parathyroid glands removed at the time of first diagnosis. This has been anecdotally advocated in some quarters as a means to improve the likelihood of success when performing parathyroidectomies in cases of PHPT where absolute certainty in identification of the offending gland has not been achieved. Unfortunately, this patient was one that later developed recurrence in the only remaining parathyroid gland. This leads us to question the merits of this approach in Keeshonden, as if they are inherently more likely to develop recurrence and therefore require repeat surgeries, there is potentially an advantage in preserving as much parathyroid tissue as possible in order to mitigate the risk of development of hyperplasia or an adenoma in the single remaining parathyroid gland. Removal of a fourth and final parathyroid gland is likely to result in significantly greater post-operative challenges with respect to calcium homeostasis, and would very likely mandate lifelong treatment with vitamin D analogues with or without dietary calcium supplementation. Although this represents a feasible way of managing hyperparathyroidism, patients with no remaining parathyroid tissue can become severely hypocalcaemic (as occurred in one patient in this study when parathyroid tissue remained but was suppressed by severe hypercalcaemia of long duration) and can be somewhat challenging to
maintain as normocalcaemic for the rest of their lifetime in some cases. Hypocalcaemia is considerably more acutely dangerous for canine patients than mild-to-moderate hypercalcaemia, and although patients with chronic hypercalcaemia have a documented increased risk of calcium-containing urolithiasis, chronic supplementation with vitamin D analogues is also associated with increased predisposition to calcium-containing urolithiasis in people, in whom hypoparathyroidism is associated with significant morbidity and poor quality of life. Furthermore, excessive vitamin D supplementation in iatrogenic hypoparathyroidism can lead to both hypercalcaemia and hyperphosphataemia, increasing the risk of tissue mineralisation and acute kidney injury. In contrast, although frequently cited as a consequence of chronic hypercalcaemia, chronic kidney disease and renal mineralisation are a very uncommon sequelae of primary hyperparathyroidism, potentially due in part to the high prevalence of sub-normal circulating phosphate. As such we would posit that removal of all parathyroid glands as an approach to treatment of PHPT is not indicated in Keeshonden. Further consideration should also be given to the timing of parathyroidectomy in Keeshonden. Based on the increased likelihood of recurrence found in this study, it may be prudent to delay surgery in Keeshonden with mild, subclinical PHPT where the mild hypercalcaemia may be suppressing the likelihood of further adenoma development. There is currently insufficient data to suggest cut-offs for calcium or ionised calcium above which surgery should be pursued, and certainly there are multiple factors involved in determining the pathogenicity of hypercalcemia over and above the absolute value. In cases where urolithiasis or mineralisation is occurring, or where there was concern over the stability of excitable membranes, then surgery would be recommended immediately, however in patients with no detectable clinical consequences there may be a reduction in the number of required surgeries over a lifetime if treatment is delayed. In humans with PHPT, surgery is indicated once total serum calcium is 0.25 mmol/L above the specific reference interval. Development of compromised renal function or urolithiasis are also indicators to pursue a surgical approach, and monitoring of reduction in bone density is also employed for this purpose. Twenty-
four-hour urine calcium excretion testing is also of use in FHH. Further work is required to characterise this in veterinary medicine.

Previous arguments for performing surgery early have centred around the risk of renal mineralisation and progressive renal damage. However, a study of 210 dogs with PHPT and 200 control dogs found that the incidence of azotemia was significantly higher in control dogs than those with PHPT, casting substantial doubt on this as a theory and as a justification for early intervention. Whilst a risk of development of mineralisation and azotemia undoubtedly exists (one Keeshond in this study was euthanised 10 months following surgery due to deterioration in renal function), it does not appear to be a consistent finding, with a reported prevalence of 3%, and therefore may not mandate immediate surgical treatment.

A further implication of the higher than previously reported rates of recurrence pertains to regularity and duration of follow up. The demonstration of a non-Keeshond dog with recurrence of PHPT means that long term periodic rechecking of total and ionised calcium levels should be recommended in all dogs that have been successfully treated. The length of time between treatment and recurrence is variable, however in one patient recurrence only occurred 6 years after the first surgery, and therefore 6-12 monthly rechecks should be recommended for all patients lifelong. This is in-line with medically managed patients in human medicine and those who have undergone surgical parathyroidectomy. The mean length of time between initial disease and recurrence in the study in Keeshonden was found to be 41 months, and therefore more frequent monitoring of calcium levels may be advisable for the first three years.

This study has several limitations. The retrospective nature of the study precludes standardisation of the follow up and monitoring of cases, making reliable assessment of relapse very challenging.

Relapse was based on redevelopment of hypercalcemia with either documentation of increased PTH or imaging or genetic testing or histopathological evidence of the development of a further adenoma. Although this means that cases diagnosed with recurrence are likely to be true cases, the
irregular testing and follow up in some cases managed at their primary practice means that the absence of recurrence cannot be guaranteed in all other cases.

The group sizes in the study are also relatively small. To mitigate the effect of this, multiple statistical tests were performed to bolster the evidence for a significant difference, and the previously described Yates correction was applied to the Chi squared test to improve reliability of analysis with small group sizes. Despite the Yates correction increasing the reported P value, it remained below the threshold for significance. A further, larger prospective study would be highly desirable to confirm these findings.

Conclusion

Recurrence of PHPT after successful treatment by parathyroidectomy is significantly more common in Keeshonden (50% recurrence rate) than in non-Keeshond dogs (7% recurrence rate). This may have implications on time and type of surgery recommended in Keeshonden with PHPT, and also reinforces the requirement for lifelong periodic screening of all dogs treated in this manner. Significant further work is required to generate clinical recommendations with regard to treatment in Keeshonden with PHPT.

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Informed Consent

Informed Consent (either verbal or written) was obtained from the owner or legal guardian of all animal(s) described in this study for the procedure(s) undertaken.

For any animals or humans individually identifiable within this publication, Informed Consent for their use in the publication (verbal or written) was obtained from the people involved.

References


