End-Stage Renal Disease Related Hyperparathyroidism
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DOI:
10.33612/diss.151471102

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Effect of parathyroidectomy and cinacalcet on quality of life in patients with end-stage renal disease related hyperparathyroidism – a systematic review

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Abstract

Background
Patients with end-stage renal disease (ESRD) have a decreased quality of life (QoL), which is in part attributable to ESRD-related hyperparathyroidism (HPT). Both cinacalcet and parathyroidectomy (PTx) are treatments for advanced HPT, but their effects on QoL are unclear. We performed a systematic review to evaluate the impact of cinacalcet and PTx on QoL.

Methods
A systematic literature search was performed using PubMed and Embase databases to identify relevant articles. The search was based on the following keywords: “parathyroidectomy” or “cinacalcet”, “secondary hyperparathyroidism” or “renal hyperparathyroidism” combined with “quality of life” or SF-36” or “symptomatology”. Only studies reporting on QoL at baseline and during follow-up were included. QoL scores were extracted from the selected manuscripts and weighted means were calculated. Due to lack of available data on QoL improvement in patients using cinacalcet, a meta-analysis could not be performed.

Results
Eight articles reached our inclusion criteria. Five articles reported on the effect of PTx on QoL. All PTx studies were observational and non-controlled. The physical component scores (PCS) of SF-36 increased significantly with a weighted mean of 35.5% (p<0.05). Mental component scores (MCS) increased with 13.7% (p<0.05). Parathyroidectomy Assessment of Symptoms (PAS) scores improved from 561 preoperatively to 302 postoperatively (-259 points; -46.2%). Visual Analogue Scale (VAS) scores reduced significantly for skin itching (46.6%), joint pain (30.4%) and muscle weakness (28.7%) (p<0.05). Three studies on the effect of cinacalcet on QoL were included, including one RCT. None of these studies showed significant improvement of PCS and MCS scores.

Conclusions
PTx improves QoL in patients treated for ESRD-related HPT, whereas cinacalcet did not. The difference of impact between PTx and cinacalcet on QoL has not been compared directly.
Introduction

Deregulated mineral metabolism is a hallmark of end-stage renal disease (ESRD). Specifically, hyperparathyroidism (HPT) with hyperplastic or hypertrophic parathyroid glands occurs commonly in patients with ESRD (30-50%). Eventually HPT contributes to progressively disturbed calcium-phosphate homeostasis and eventually to autonomous PTH overproduction and hypercalcemia remaining irrespective of renal function: tertiary HPT. Clinical HPT-related manifestations vary from somatic symptoms such as fatigue and abdominal pain, to psychological symptoms such as forgetfulness, mood swings and concentration difficulties. Furthermore, HPT has been associated with versatile detrimental effects on health status, especially with respect to bone disorders, cardiovascular disease, increased risk of mortality and even reduced quality of life (QoL). QoL of ESRD patients is often already decreased both due the symptoms of ESRD itself and the burden of dialysis treatment.

In the management of HPT, different treatment modalities are available. According to the Kidney Disease Improving Global Outcome (KDIGO) guidelines patients with ESRD related HPT should initially receive medical therapy, with vitamin D analogs and phosphate binders. Upon failure of initial therapy, prescription of the calcimimetic agent cinacalcet is recommended. Cinacalcet increases the sensitivity of the calcium-sensing receptor (CaSR) located within the parathyroid glands, aiming to reduce excretion of PTH and balance calcium-phosphate homeostasis. KDIGO guidelines recommend parathyroidectomy (PTx) only in patients with severe HPT (>800 pg/mL) who are refractory to medical therapy. Since its introduction in 2004, cinacalcet has gained a dominant role in the treatment algorithm of ESRD related HPT and PTx is less often performed. However, emerging data suggest that the reticent position of surgery in the treatment algorithm of HPT might be questionable. In a previous study, we showed that PTx is a very safe and effective treatment. Furthermore, Narayan and co-authors showed that PTx is more cost-effective than cinacalcet after 7.25 months of treatment. Since no randomized controlled trial (RCT) comparing PTx with cinacalcet has been performed so far, the optimal treatment of ESRD related HPT remains unclear.

In order to provide a patient-tailored approach to HPT it is of paramount importance to also assess the effect of these interventions QoL, in line with the increasing interest in patient reported outcome measures (PROMs). It is known that PTx improves QoL in patients with primary HPT, however whether there is an additional positive effect of PTx or cinacalcet in patients with concurrent ESRD remains uncertain. Therefore, we
performed a systematic review of studies measuring QoL in patients with HPT who received cinacalcet or underwent (sub)total PTx.
Methods

Search strategy
To identify relevant articles a systematic literature search was conducted using PubMed and EMBASE. The following search terms were used to identify articles on the effect of PTx on QoL: parathyroidectomy, secondary hyperparathyroidism, tertiary hyperparathyroidism, quality of life, SF-36, symptomatology. Next, we used the following search terms to identify articles describing the effect of cinacalcet on QoL: secondary hyperparathyroidism, tertiary hyperparathyroidism, cinacalcet hydrochloride, quality of life, SF-36, symptomatology. Additionally, we searched for abstracts and unpublished studies on the websites of the FDA, EMA, ASN and EDTA. The search protocol has not been published or submitted to an ethical committee.

Article selection and data extraction
Only original research papers written in English and published between 1980 and 2015 were included for further analysis. These abstracts were screened by two independent reviewers (RD, WYvdP) and all articles complying with the following criteria were selected: (1) studies assessing QoL using any kind of health questionnaire. Both general and disease-specific questionnaires were included. (2) QoL was assessed both at baseline and during follow-up after PTx or initiation of cinacalcet in HPT patients. In case of disagreement a third reviewer was consulted (TMvG or SK). After this selection process all full text articles were studied and cross reference check was performed. Our online search yielded 277 articles, to which two articles were additionally found by cross-referencing. Eventually, five publications on PTx met the inclusion criteria and were included in this review. Three relevant manuscripts on the effect of cinacalcet on QoL were selected (Figure 1). Corresponding authors were asked to provide additional data if the articles did not contain the required information. Secondary endpoints of our analyses were biochemical measurements including parathyroid hormone (PTH), calcium and phosphate levels before and after intervention. No additional studies or abstracts were found on the websites of the FDA, EMA, ASN or EDTA.

Quality assessment
All eligible articles were independently scored regarding their quality by three reviewers blinded to each other’s results (WYvdP, RD and SK). In case of disagreement the article was discussed and a definitive score was calculated based on consensus. Case series were assessed by means of the 18-criteria checklist by the Delphi panel. This validated checklist includes the quality of the study objective, population, intervention and co-intervention,
outcome measures, and statistical analysis. A maximum of 18 points could be awarded. A score of 14-18 points was considered high-quality, a score of 9-13 fair quality. For case-control and cohort studies, the Newcastle-Ottawa scale was appraised.18 The scale consists of three domains addressing the aspects of methodology including selection, comparability and outcome (cohort studies) or exposure (case-control studies) for which stars could be allotted. A total of 9 stars could be awarded. A score of 7-9 was considered high quality, 4-6 was considered fair quality. Articles reporting a randomized controlled trial (RCT) were assessed using the CONSORT 2010 statement.19 Also, the risk of publication bias will be assessed using a funnel plot.

Quality of life and symptoms measurement tools
The Medical Outcomes Study Short-Form Health Survey® (SF-36®) is a commonly applied questionnaire of 36 simple questions on eight health domains. Each dimension can be transformed into a 0-100 scale, where a higher score represents better self-perceived well-being and QoL. These eight domains can be distinguished into two summery scores: the physical component summary score (PCS) and the mental component summary score (MCS). For both the PCS as the MCS a score of 50 represents the mean of the United States population with a standard deviation (SD) of 10. In hemodialysis patients, reported mean PCS ranges from 31.6-49.8 and MCS varies from 46.0-50.2.20-22 A change in PCS or MCS scores of minimally 2 points is thought to be clinically meaningful.23 The European Quality of Life 5 Dimensions (EQ-5D) assessment is another classification instrument. It encompasses 5 domains: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression each with three response levels.24 Pasieka et al. developed a disease-specific outcome tool for hyperparathyroidism. The Parathyroidectomy Assessment of Symptoms (PAS) is a questionnaire which contains all HPT-related symptoms initially designed for primary HPT.4 This 13-item questionnaire has been validated for secondary and tertiary HPT and is correlated to the SF-36 questionnaire.25 The visual analogue scale (VAS) ranging from 1-100 was used to assess the degree of severity per symptom. The 13 included symptoms are bone pain, fatigue, mood swings, feeling "blue" or depressed, abdominal pain, feeling weak, feeling irritable, joint pain, forgetfulness, difficulty getting out of a chair or car, headaches, itchy skin, and being thirsty. Subsequently, a maximum PAS score of 1,300 can be reached.

Statistics
Mean QoL scores were extracted from the selected manuscripts. Weighted means were calculated as follows: (number of patients * the mean score difference) / total number of patients.
Results

Description and quality of the included studies

A description of the included studies is shown in Table 1. Of the five included studies on PTx, four articles provided SF-36 scores, three of which reported the summary scores. Two papers also assessed quality of life by means of the PAS score and one article used a general VAS system. There were no multicenter studies and follow-up ranged from 3-12 months. All studies stated a complete objective and/or hypothesis and outcome measures were clearly described in all studies. In 80% of the studies patients had been recruited consecutively. All studies reported length of follow-up, but only one of the five studies mentioned the number of participants lost to follow-up. All authors drew conclusions fully supported by their results. We considered 3 articles to be of high quality and 2 of fair quality.

Three studies reporting the effect of cinacalcet on QoL were included. One was based on the EVOLVE trial, a multicenter RCT comparing cinacalcet with placebo. All manuscripts stated clear hypotheses and endpoints were fully described. The risk of publication bias could not be tested since <10 studies were included in this analysis.
Effect of parathyroidectomy on quality of life
All studies reported significant improvement in QoL after PTx (Table 2). These positive effects were reported both after short-term (3 months) and longer-term follow-up (12 months). The weighted mean physical component scores were 33.2 preoperatively and increased significantly to 45.3 postoperatively (weighted mean increase of 35.5%). The mental component scores increased from 44.6 preoperatively to 50.9 postoperatively (+13.7%). PAS scores improved from 561.5 preoperatively to 302.3 postoperatively (-259 points, -46.2%). Yang et al. reported VAS scores on three domains: skin itching, joint pain and muscle weakness. Pain scores of these items reduced significantly by 46.6%, 30.4% and 28.7%, respectively.

In the study by Yang et al., the MCS slightly decreased 1 month postoperatively compared with the preoperative situation.

Effect of cinacalcet on quality of life
Filipozzi et al. (n=124) reported absolute values. At baseline, PCS and MCS scores were 38.6 ± 5.3 and 45.5 ± 7.4 respectively. At the end of follow-up, PCS score was 38.7 ± 5.3 and MCS score 44.6 ± 7.7. No p-value was provided. Briggs et al. (n=1780) reported QoL data expressed as EQ-5D scores. The estimated treatment effect of cinacalcet at the end of follow-up did not reach statistical significance compared to placebo. Chertow and co-authors analyzed 567 patients who participated in an open-label clinical trial that showed that cinacalcet had a significant positive effect on 4 of 14 related symptoms at the end of study (dry skin, ache in bones, joint pain, and trouble with memory). However, no significant changes were seen in PCS and MCS scores both at the end of the efficacy assessment (16-22 weeks) and at end of follow-up (12 months).
Effect of parathyroidectomy and cinacalcet on quality of life in patients with end-stage renal disease-related hyperparathyroidism – a systematic review

Table 1 - Characteristics of the included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Patient population</th>
<th>No. of patients</th>
<th>Study design</th>
<th>Follow-up</th>
<th>Age (M/F)</th>
<th>Sex</th>
<th>Baseline PTH (pg/mL)*</th>
<th>Quality appraisal</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTx</td>
<td></td>
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<tr>
<td>Bratuca²⁶</td>
<td>2015</td>
<td>ESRD patients who would undergo PTx for HPT</td>
<td>85</td>
<td>Case series</td>
<td>6 months</td>
<td>51 ± 12</td>
<td>39/46</td>
<td>1379 (414-3345)</td>
<td>High (15/18)†</td>
</tr>
<tr>
<td>Cheng²⁷</td>
<td>2013</td>
<td>ESRD patients with HPT scheduled for PTx</td>
<td>49</td>
<td>Case series</td>
<td>12 months</td>
<td>52 ± 11</td>
<td>18/31</td>
<td>1416 ± 449</td>
<td>Fair (13/18)†</td>
</tr>
<tr>
<td>Yang²⁷</td>
<td>2011</td>
<td>ESRD patients who would undergo PTx for advanced HPT</td>
<td>37</td>
<td>Case series</td>
<td>3 months</td>
<td>55 ± 12</td>
<td>18/31</td>
<td>2086 ± 1452</td>
<td>Fair (11/18)†</td>
</tr>
<tr>
<td>Chow²⁸</td>
<td>2003</td>
<td>ESRD patients who would undergo PTx for advanced HPT</td>
<td>12</td>
<td>Case series</td>
<td>6 months</td>
<td>50 ± 11</td>
<td>5/7</td>
<td>2320 ± 215</td>
<td>High (14/18)†</td>
</tr>
<tr>
<td>Pasieka and</td>
<td>2000</td>
<td>ESRD patients with HPT scheduled for PTx</td>
<td>32</td>
<td>Case control</td>
<td>12 months</td>
<td>45 (23-66)</td>
<td>14/18</td>
<td>909 (131-1514)</td>
<td>High (8/9)‡</td>
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<tr>
<td>Parsons³</td>
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<tr>
<td>Cinacalcet</td>
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<tr>
<td>Chertow²⁹</td>
<td>2012</td>
<td>ESRD patients with HPT</td>
<td>567</td>
<td>Clinical trial</td>
<td>12 months</td>
<td>55 ± 14</td>
<td>294 (172-655)</td>
<td>High (14/18)‡</td>
<td></td>
</tr>
<tr>
<td>Briggs³⁰</td>
<td>2016</td>
<td>ESRD patients with HPT</td>
<td>1780</td>
<td>Double-blind RCT study</td>
<td>64 months</td>
<td>55 ± 15</td>
<td>N.A.</td>
<td></td>
<td>Fair (14/25)‡</td>
</tr>
<tr>
<td>Filipozzi³¹</td>
<td>2014</td>
<td>ESRD patients with HPT</td>
<td>124</td>
<td>Cohort study</td>
<td>12 months</td>
<td>67 ± 15</td>
<td>72/52</td>
<td>622 ± 161</td>
<td>High (8/9)‡</td>
</tr>
</tbody>
</table>

† 18-criteria checklist by the Delphi panel
‡ Newcastle-Ottawa scale
∫ CONSORT 2010 statement
* Data is shown as mean ± standard deviation or median (interquartile range)
RCT, randomized controlled trial; N.A., not available.
Figure 2 – Quality of Life measurements in patients who underwent PTx

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No. of patients</th>
<th>Follow-up</th>
<th>Main objective</th>
<th>Pre PTx</th>
<th>Post PTx</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SF-36</strong></td>
<td></td>
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<tr>
<td>Bratucu(^{a})</td>
<td>2015</td>
<td>85</td>
<td>6 months</td>
<td>SF-36</td>
<td>29.96 ± 8.11</td>
<td>38.50 ± 5.36</td>
<td>&lt;0.0001</td>
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<td></td>
<td>45.06 ± 11.37</td>
<td>47.28 ± 9.30</td>
<td>0.01</td>
</tr>
<tr>
<td>Cheng(^{a})</td>
<td>2013</td>
<td>49</td>
<td>12 months</td>
<td>SF-36</td>
<td>40.3 ± 17.1</td>
<td>59.0 ± 14.9</td>
<td>&lt;0.0001</td>
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<td></td>
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<td></td>
<td>47.6 ± 17.1</td>
<td>63.7 ± 13.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yang(^{a})</td>
<td>2011</td>
<td>37</td>
<td>3 months</td>
<td>SF-36</td>
<td>31.3 (20 – 45.1)</td>
<td>42.9 (27.7 – 48.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
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<td>39.5 (25 – 48.6)</td>
<td>42.4 (29.8 – 49.2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Chow(^{a})</td>
<td>2003</td>
<td>12</td>
<td>6 months</td>
<td>SF-36</td>
<td>59.2 ± 26.8</td>
<td>68.0 ± 28.6</td>
<td>0.01</td>
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<td></td>
<td>27.1 ± 31.0</td>
<td>50.0 ± 46.5</td>
<td>0.04</td>
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<td></td>
<td>57.9 ± 27.8</td>
<td>83.1 ± 16.3</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>PAS</strong></td>
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<tr>
<td>Bratucu(^{a})</td>
<td>2015</td>
<td>85</td>
<td>6 months</td>
<td>PAS</td>
<td>567 ± 136</td>
<td>293 ± 85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cheng(^{a})</td>
<td>2013</td>
<td>49</td>
<td>12 months</td>
<td>PAS</td>
<td>545 ± 263</td>
<td>284 ± 201</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pasieka and</td>
<td>2000</td>
<td>32</td>
<td>12 months</td>
<td>Median symptom index score</td>
<td>572</td>
<td>355</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Parsons(^{a})</td>
<td></td>
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<tr>
<td><strong>VAS</strong></td>
<td></td>
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<tr>
<td>Yang(^{a})</td>
<td>2011</td>
<td>37</td>
<td>3 months</td>
<td>VAS</td>
<td>4.31 ± 3.33</td>
<td>3.0 ± 2.19</td>
<td>&lt;0.001</td>
</tr>
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<td></td>
<td></td>
<td>4.98 ± 3.37</td>
<td>2.61 ± 2.19</td>
<td>&lt;0.05</td>
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<td></td>
<td>4.63 ± 2.90</td>
<td>3.30 ± 2.19</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results are reported as mean ± SD or median (25th – 75th percentile)
Discussion

This is the first systematic review to examine the impact of PTx and cinacalcet for the treatment of HPT on QoL. Eight peer-reviewed studies published between 2000-2015 were analyzed. Patients with secondary and tertiary hyperparathyroidism who underwent PTx experienced a significant improvement of QoL. Cinacalcet on the other hand, did not convincingly have a positive effect on QoL.

HPT develops in 30-50% of all patients with ESRD. It is well recognized that ESRD and accompanying complications are associated with polypharmacy, a decreased life expectancy, and a reduced QoL. Strikingly, only few studies assessed the effect of PTx and cinacalcet on QoL as an endpoint in the fragile ESRD population. In this review we summarized available data related to the impact of PTx and cinacalcet on QoL in ESRD patients with HPT. Our data suggest that PTx might improve QoL in these patients, whereas cinacalcet does not seem to influence QoL.

The improvement of QoL after PTx is probably caused by the resection of almost all parathyroid tissue, resulting in a strong correction of PTH overproduction. Due to the extremely short half-life of PTH (<2 min.) serum PTH drops immediately, leading to low serum PTH levels. In line, HPT related symptoms as described by Pasieka et al., such as bone pain, fatigue and depression diminish almost directly after PTx. It should be noted that none of the included articles on the effect of PTx were sham-controlled. It is likely that bias introduced by the lack of sham-controlled surgery plays a substantial role in the improvement patients experienced after PTx. Thus, although the individual studies in our meta-analysis were considered to be of reasonable to good quality, the level of evidence to support the effect of PTx on QoL remains low. On the other hand, patients require less medications after surgery, which also benefits QoL.

Several studies have investigated the influence of cinacalcet on QoL of the ESRD patient population. These studies showed less promising results when compared to the QoL improvement after PTx. Our findings are in line with data by Cunningham et al., who undertook a compared analysis of four unpublished RCTs that QoL in patients with HPT treated with either cinacalcet (n=665) or placebo (n=471). The main outcome was that only two (bodily pain and general health) of the eight domains of SF-36 improved significantly in the cinacalcet group compared to the control group with a difference of less than two points, while only a difference of 3 to 5 points is considered clinically meaningful. The fact that cinacalcet does not seem effective in improving QoL may at
least partly be explained by the occurrence of side effects such as nausea, vomiting, and diarrhea that may counteract potential QoL improvements due to PTH lowering.\textsuperscript{26} We found no study comparing the effects on QoL of cinacalcet with PTx directly.

The strength of this systematic review is our methodological approach. After establishing a well-designed reproducible search string in collaboration with an experienced medical librarian, the selection and analysis were conducted by three individual reviewers. Afterwards, selected manuscripts were assessed on their quality using validated quality assessment tools also independently by three authors. This assessment indicates that all studies were of enough quality to address our question. Limitations of this review are inherent to the study population. QoL is influenced by many factors and it remains difficult to assess the true benefit of surgery alone in the absence of sham-controls. In addition, data is limited and unfortunately, no meta-analysis was possible. Due to lack of data, we could not test the risk for publication bias. However, we do acknowledge the potential risk for publication bias, which should be taken into account when interpreting the results. Lastly, a search protocol has not been published or presented to an ethical committee.

Since the availability of calcimimetics, in daily practice PTx is now only indicated in patients with uncontrollable HPT.\textsuperscript{10} Meanwhile, in the last decade the quality of parathyroid surgery has improved with the use of less invasive operations, heat sealing devices and improved imaging for preoperative localization.\textsuperscript{33,34} Notwithstanding, PTx remains a surgical procedure executed in a fragile population with cause-specific morbidity, including hypocalcaemia, emergency admissions (myocardial dysrhythmias, cerebrovascular events) as described in a large nationwide US study.\textsuperscript{35} These data might explain the hesitance of nephrologists to refer their patients for surgery and their increased motivation for treatment with cinacalcet.\textsuperscript{36} The intravenous calcimimetic etelcalcetide was recently approved by the European Medicines Agency and will become available on the European market in 2017, which may provide a further impulse for upfront medical management of HPT.\textsuperscript{37} On the other hand, we demonstrated that PTx is a safe procedure with low complication rates when performed in a tertiary referral center. Postoperative complications, including surgical site problems (3.5%), temporary recurrent laryngeal nerve damage (1.8%) and intensive care admissions (0.8%) were rare. Postoperative hypocalcaemia was seen 39.8% of the patients.\textsuperscript{13} This difference might indicate the necessity of referring these fragile patients to high-volume centers. Despite data indicating that surgical intervention is highly effective, has a positive effect on QoL, and is safe when performed in an experienced center, pharmacological treatment has
so far remained the first-line treatment for advanced HPT. In order to ultimately compare the short-term and long-term effects of cinacalcet and PTx on QoL in HPT patients both short-term as well as long-term, a randomized controlled trial (RCT) soon will be conducted (EudraCT no. 2016-002174-12). Along with results of comparing biochemical effects and cost-effectiveness, recommendations for renewed guidelines should be established.

Parathyroidectomy improves quality of life in patients treated for ESRD-related HPT, whereas cinacalcet did not. In order to provide a patient tailored-approach for the treatment of HPT biochemical, clinical and quality of life changes must be taken into account.
References


Effect of parathyroidectomy and cinacalcet on quality of life in patients with end-stage renal disease-related hyperparathyroidism – a systematic review


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