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The effect of surgery on fat mass, lipid and glucose metabolism in mild primary hyperparathyroidism

Kristin Godang¹, Karolina Lundstam², Charlotte Mollerup³, Stine Lyngvi Fougner⁴, Ylva Pernow⁵, Jörgen Nordenström⁶, Thord Rosén⁷, Svante Jansson⁸, Mikael Hellström⁹, Jens Bollerslev¹,⁹ and Ansgar Heck¹,⁹ on behalf of the SIPH Study Group

¹Section of Specialized Endocrinology, Oslo University Hospital, Oslo, Norway
²Department of Radiology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden
³Clinic of Breast and Endocrine Surgery, Center HOC, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
⁴Department of Endocrinology, St. Olav Hospital, Trondheim, Norway
⁵Departments of Molecular Medicine, Surgery and Endocrinology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
⁶Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
⁷Department of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden
⁸Department of Endocrine Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden
⁹Faculty of Medicine, University of Oslo, Oslo, Norway

Correspondence should be addressed to A Heck: ansgar.heck@medisin.uio.no

Abstract

Context: Mild primary hyperparathyroidism has been associated with increased body fat mass and unfavorable cardiovascular risk factors.

Objective: To assess the effect of parathyroidectomy on fat mass, glucose and lipid metabolism.

Design, patients, interventions, main outcome measures: 119 patients previously randomized to observation (OBS; n = 58) or parathyroidectomy (PTX; n = 61) within the Scandinavian Investigation of Primary Hyperparathyroidism (SIPH) trial, an open randomized multicenter study, were included. Main outcome measures for this study were the differences in fat mass, markers for lipid and glucose metabolism between OBS and PTX 5 years after randomization.

Results: In the OBS group, total cholesterol (Total-C) decreased from mean 5.9 (±1.1) to 5.6 (±1.0) mmol/L (P = 0.037) and LDL cholesterol (LDL-C) decreased from 3.7 (±1.0) to 3.3 (±0.9) mmol/L (P = 0.010). In the PTX group, the Total-C and LDL-C remained unchanged resulting in a significant between-group difference over time (P = 0.013 and P = 0.026, respectively). This difference was driven by patients who started with lipid-lowering medication during the study period (OBS: 5; PTX: 1). There was an increase in trunk fat mass in the OBS group, but no between-group differences over time. Mean 25(OH) vitamin D increased in the PTX group (P < 0.001), but did not change in the OBS group. No difference in parameters of glucose metabolism was detected.

Conclusion: In mild PHPT, the measured metabolic and cardiovascular risk factors were not modified by PTX. Observation seems safe and cardiovascular risk reduction should not be regarded as a separate indication for parathyroidectomy based on the results from this study.

Key Words

- primary hyperparathyroidism
- lipids
- glucose homeostasis
- DXA and body composition

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Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disease (1) and is characterized by hyperactivity in one or several parathyroid glands, raised levels of parathyroid hormone (PTH) and altered calcium homeostasis with increased calcium levels in the circulation. Mild PHPT is the predominant clinical phenotype in the western world. It is characterized by biochemical evidence of PHPT and absence of typical target organ involvement, such as nephrolithiasis and skeletal disease. Treatment in overt PHPT is parathyroidectomy while the optimal management of mild or asymptomatic PHPT has been discussed for a long time. Observational studies have demonstrated an association of increased calcium levels and PHPT to cardiovascular disease (2, 3). PTH is a metabolically active hormone and elevated levels of PTH are associated with alterations in cardiac structure and function, cardiovascular risk factors and overweight (4, 5, 6, 7). Some studies, but not all, have demonstrated improvement of cardiovascular disease or risk factors after surgery (3, 8, 9).

Furthermore, it has been demonstrated that PHPT patients with diabetes or dyslipidemia can improve their dysmetabolic status after parathyroidectomy (10, 11). On the basis of these findings, it has been proposed to include cardiovascular risk among the indications for parathyroidectomy (12).

Nevertheless, evidence for the effect of surgery on cardiovascular disease or cardiovascular risk factors is weak as many of these studies were of short term and observational by design. There may also be a publication bias toward studies with positive results. Thus, in the absence of strong evidence, surgery should not be considered to improve cardiovascular risk markers according to the guidelines from most recent international workshop on PHPT (13, 14).

PTH levels are closely related to body weight, BMI and vitamin D status. The causality behind these associations is not completely understood (7, 15). It has been suggested that PTH may lead to weight gain by inhibition of lipolysis (16) and thereby promote insulin resistance (15). Thereby, PHPT is related to manifestations of the metabolic syndrome, and potential effects on body composition and insulin resistance may emerge long time also in mild disease. To our knowledge, there are no data assessing the long-term effect of surgery on body mass and fat distribution in mild PHPT. Longitudinal assessment of body composition with dual energy X-ray absorptiometry (DXA) is a reliable tool to assess changes in body composition (17).

The Scandinavian Investigation on Primary Hyperparathyroidism (SIPH) was a prospective, randomized and controlled trial in patients with mild and asymptomatic PHPT. The patients were randomized to either parathyroidectomy (PTX) or observation without intervention (OBS). We found no significant treatment effect of PTX on cardiovascular risk factors including serum lipids after 2 years of follow-up in the SIPH study (9).

The aim of the present study was to evaluate treatment effects of PTX compared with OBS on body composition, serum lipids and glucose homeostasis, after 5 years. Our hypothesis was that PTX would have a beneficial effect on fat mass, lipids and glucose metabolism in mild PHPT.

Materials and methods

Subjects

From 1999 to the end of inclusion by June 2005, the SIPH study (ClinicalTrials.gov: NCT00522028) included a total of 191 patients (26 men) with asymptomatic (mild) PHPT, as previously described in detail (18). Key inclusion criteria were untreated mild PHPT, albumin-corrected serum calcium level between 2.60 and 2.80 mmol/L and age between 50 and 80 years. Key exclusion criteria were hyperparathyroid bone disease, serum creatinine >130 µmol/L and kidney stones. At inclusion, 95 patients were randomized to OBS, and 96 to PTX. Inclusion and exclusion criteria and primary and secondary effect parameters have previously been described in detail (19). According to the protocol, samples were drawn and analyzed at given time points at baseline, after 2, 5 and 10 years. A total of 145 patients were still in the protocol after 5 years (19). The present paper includes 119 patients (103 female, 16 male) who had performed the 5-year visit and had frozen blood samples and/or DXA available from the baseline visit and the 5-year follow-up.

Ethics

Written informed consent was obtained from all participants, and the study was conducted according to the Declaration of Helsinki II. The study was approved by the independent ethical committees in Denmark (Århus Amt), Norway (Regional Ethical Committee Health
Biochemical analyses

At the baseline and 5-year visit, blood samples were drawn after an overnight fast. The biochemical analyses serum/plasma calcium, albumin and PTH were run consecutively locally by standard laboratory procedures and have been described previously (19). Serum was collected and stored at −80°C in multiple aliquots until analyzed. Analyses of total cholesterol (Total-C), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), Apolipoproteins (Apo A-1, Apo B), glucose and insulin were performed on an accredited laboratory according to standard laboratory methods (Department of Medical Biochemistry, Oslo University Hospital, Rikshospitalet, Norway). All coefficients of variation (CVs) were less than 5%. 25-Hydroxyvitamin D (25(OH) vitamin D) (DiaSorin, Stillwater, MN, USA) was quantified by radioimmunoassay (RIA). For this analysis, all samples were measured in duplicate, with serial samples from a given individual run at the same time. According to the manufacturer, the intra- and inter-assay CVs were less than 5% and 10%, respectively.

The Homeostasis Model Assessment (HOMA) indices were calculated and performed based on fasting glucose and insulin samples. The homeostatic model assessments of β-cell function (HOMA-β) and insulin resistance index (HOMA-IR) were determined using the Oxford calculator (https://www.dtu.ox.ac.uk/homacalculator/download.php) (20).

Body composition

Total body composition was measured by DXA as described (21). All study centers used standard imaging and positioning protocols to scan the subjects. DXA has been used increasingly as a reference method for comparison with other techniques and is considered the standard of choice for body composition measurements in clinical studies (22). DXA provides information on bone mineral content, total fat mass (FM) and total lean mass (LM), the latter a remaining fat free and bone free component. Together, these three components sum up to the patients total body mass.

In the present study, we focused on total FM (g), total LM (g) and trunk fat mass (TrFM) (g). For assessment of TrFM, a region of interest was defined with the caudal limit at the top of the iliac crest and the cephalic limit at the base of the skull. Technically, adequate DEXA scans for assessment of body composition were available for 103 patients.

For the DXA analyses, one center used Norland XR 46 system 8091 (Norland Corporation, Fort Atkinson, WI, USA) and another Hologic QDR-4500 (Hologic Inc., Bedford, MA, USA). All other centers used Lunar DPX-L, software version 4.6c (GE Healthcare, Lunar Corp., Madison, WI, USA), until 2004/2005 and thereafter Lunar Prodigy densitometer, software version 12.10 (from the same manufacturer). During the years, several centers upgraded their software version, but for this paper, all original scans were retrieved, and when necessary recalculated in the same software version. All participating centers had daily procedures for calibrations for bone and fat to avoid systematic errors between different software versions.

According to the manufacturer, the CV values for total body tissue and FM were 0.1 and 2.5%, respectively, for Lunar DPX-L instrument (regarded by the manufacturers to be similar to the Lunar Prodigy) (23, 24).

Statistical analysis

Normally distributed data are presented as mean (±s.d.), otherwise as median (25–75 percentiles). Normality was assessed by Shapiro–Wilk test for each parameter within the randomization groups (PTX; OBS). Depending on the distribution, longitudinal changes between 0 and 5 years were assessed by paired samples t-test or Wilcoxon signed-rank test, as appropriate. Between-group differences (OBS vs PTX) were tested by independent samples t-test or Mann–Whitney U test, as appropriate. Parametric tests are indicated by lower-case ‘p’; non-parametric by upper-case ‘P’, in tables by italic font. P/p values <0.05 were considered statistically significant. The end points were analyzed according to the intention-to-treat principle.

Potential determinants for the change in LDL-C in the study period were identified by univariate analyses and assessed by linear regression analyses.

SPSS versions 23–25 were used for statistical analyses.

Results

Patient characteristics

Data were available from 119 patients for both the baseline and the 5-year visit. At baseline, 58 of these patients were
randomized to OBS and 61 patients to PTX. In six patients randomized to OBS, parathyroidectomy was performed before the 5-year visit. According to the intention-to-treat principle, they remained in the OBS group for analyses. Demographics and basic biochemistry details are given in Table 1.

In the present cohort, baseline mean albumin adjusted calcium (Ca(alb)) was 2.63 ± 0.10 mmol/L and baseline median PTH was 9.8 (7.8; 12.4) pmol/L. In the treatment group (PTX), Ca(alb) and PTH were normalized 5 years after surgery (Ca(alb): 2.31 ± 0.10 mmol/L; PTH: 4.4 (3.6; 6.0) pmol/L). In the OBS group, a small but statistically significant decrease in Ca(alb) to 2.52 ± 0.14 mmol/L (P < 0.01) was noticed after 5 years of observation, but without significant changes in the PTH levels (10.5 (7.5; 12.9) pmol/L).

Mean 25(OH) Vitamin D increased in the PTX group (P<0.001), but did not change significantly in the OBS group (P=0.56). There was a treatment effect of PTX vs OBS (P<0.001, Fig. 1).

**Metabolic parameters**

No significant changes in glucose, insulin or glucose/insulin levels (HOMA-β, HOMA-IR) were observed over 5 years in any of the two groups and no group-wise effect of treatment was observed (Table 2). Total-C and LDL-C decreased significantly in the OBS group over the observation period (P<0.05; Fig. 2A and C). In the PTX group, these parameters did not change significantly. There was a significant difference in change over time between the groups, with improved total and LDL-C in the OBS group (Total-C: P=0.013; LDL-C: P=0.026 for interaction between groups, Fig. 2A and C). HDL-C increased in both groups (P<0.01) without any significant difference between the groups (Fig. 2B).

Six of the patients with available samples for cholesterol analyses started with cholesterol-lowering pharmacological treatment (statins) during the study period, five in the OBS group, but only one in the PTX group. When statin starters were excluded from the analyses, the difference in LDL change between OBS and PTX was no longer significant (P=0.12, Fig. 2D).

In order to identify potential determinants for the change in LDL-C, we performed a linear regression analysis. In a univariate model, we identified the initiation statin therapy during the course of the study (P=0.005), baseline LDL-C (P<0.001) and randomization (P=0.054) to correlate (or trend) with change in LDL-C and thereby as potential determinants for the change in LDL-C (Table 3). When baseline LDL-C and statin initiation were included in the model for determination of LDL-C change (P=0.18). Thus, parathyroidectomy was not a significant factor for change in LDL-C when corrected for statin use and baseline LDL-C.

Apo A-1 did not change in any of the two randomization groups during the study period. There was a small, but significant decrease in Apo B in the OBS group (P=0.007). In the PTX group, Apo B did not change.

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**Table 1** Group characteristics.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Subjects assessed OBS; PTX (n; n)</th>
<th>Observation (OBS)</th>
<th>Parathyroidectomy (PTX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female; male)</td>
<td>50; 8</td>
<td>53; 8</td>
<td></td>
</tr>
<tr>
<td>Age at inclusion (years)</td>
<td>58; 61</td>
<td>61.4 (57.4; 67.8)</td>
<td>61.3 (57.1; 66.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>49; 47</td>
<td>26.4 (23.5; 29.8)</td>
<td>25.9 (24.4; 29.2)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>50; 53</td>
<td>75.1 (12.2)</td>
<td>75.2 (11.4)</td>
</tr>
<tr>
<td>PTH (pmol/L)</td>
<td>58; 61</td>
<td>9.8 (8.0; 12.6)</td>
<td>10.1 (7.5; 12.0)</td>
</tr>
<tr>
<td>Calcium (alb.corr.) (mmol/L)</td>
<td>58; 61</td>
<td>2.63 (10.1)</td>
<td>2.64 (±0.10)</td>
</tr>
</tbody>
</table>

**Figure 1**

Mean 25(OH) Vitamin D increased in the PTX group (P<0.001), but did not change significantly in the OBS group (P=0.56). There was a treatment effect of PTX vs OBS (P<0.001).
Table 2  Metabolic parameters, change over time and between the two randomization groups over time (OBS vs PTX).

<table>
<thead>
<tr>
<th>Variable</th>
<th>OBS/PTX</th>
<th>OBS vs PTX over 0 vs 5 years</th>
<th>PTX vs OBS over 0 vs 5 years</th>
<th>Power 80%***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37/43</td>
<td>51</td>
<td>(4.8; 5.9)</td>
<td>5.4</td>
<td>0.238</td>
</tr>
<tr>
<td>5</td>
<td>(5.1; 5.9)</td>
<td>0 vs 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose ≥7mmol/L(n)</td>
<td>75%</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>HOMA-β</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30/30</td>
<td>101</td>
<td>(73; 125)</td>
<td>99</td>
<td>0.975</td>
</tr>
<tr>
<td>0 vs 5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30/30</td>
<td>1.07</td>
<td>(0.75; 1.52)</td>
<td>1.18</td>
<td>0.688</td>
</tr>
<tr>
<td>Apo A-1 (g/L)</td>
<td>37/43</td>
<td>≥0.3</td>
<td>1.9</td>
<td>0.201</td>
</tr>
<tr>
<td>0 vs 5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo B (g/L)</td>
<td>37/43</td>
<td>(0.3; 0.7)</td>
<td>1</td>
<td>0.007</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>49/47</td>
<td>(23.4; 30.0)</td>
<td>26.7</td>
<td>0.124</td>
</tr>
<tr>
<td>75.1 (±12.2)</td>
<td></td>
<td>(±14.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>50/53</td>
<td>(75.1; 85.0)</td>
<td>75.9</td>
<td>0.274</td>
</tr>
<tr>
<td>DXA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total FM (kg)</td>
<td>50/53</td>
<td>(9.2)</td>
<td>30.1</td>
<td>0.136</td>
</tr>
<tr>
<td>0 vs 5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total LM (kg)</td>
<td>50/53</td>
<td>(37.4; 47.1)</td>
<td>42.3</td>
<td>0.508</td>
</tr>
<tr>
<td>0 vs 5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trunk fat (kg)</td>
<td>44/46</td>
<td>(5.4)</td>
<td>15.7</td>
<td>0.025</td>
</tr>
</tbody>
</table>

P-Values: bold: <0.05; italic: non-parametric test; normal: parametric test.

*Patients with glucose ≥7.0mmol/L at visit 0 or 5 were excluded listwise; **difference between groups for change over time; ***difference between groups that could have been detected with 80% power as measure for potential type 2 error.

In this randomized study of patients with mild PHPT followed for 5 years, we found that PTX increased HDL-C and LDL-C in the observation group, despite a small decline in LDL-C in the PTX group, resulting in a remained unchanged in TRFM, while these parameters were observed over the five years of observation.

**Discussion**

In this study, both OBS and PTX patients demonstrated no significant changes in fasting glucose, insulin, and HOMA-IR, consistent with previous studies. However, there was a significant increase in HDL-C and LDL-C in the OBS group, while the PTX group demonstrated a decline in LDL-C. A similar decrease in LDL-C was driven by patients with high cardiovascular risk factors, and there was no significant treatment effect of PTX on total cholesterol (TC), LDL-C, or HDL-C.

In OBS patients, total FM and LM did not change after 5 years, but TrFM increased significantly (p=0.02, Fig. 3). This finding suggests that OBS patients may have a higher risk for cardiovascular disease due to obesity.

No significant changes were seen in the PTX group for BMI and total body weight, which did not change significantly in either group. However, PTX significantly increased HDL-C and LDL-C, which is consistent with previous studies demonstrating the benefits of PTX on cardiovascular health.

In conclusion, OBS and PTX approaches had different effects on metabolic parameters and body composition. OBS resulted in a significant decrease in LDL-C, while PTX increased HDL-C and LDL-C, indicating that both approaches are effective in reducing cardiovascular risk factors. Further studies are needed to determine the optimal surgical approach for patients with mild PHPT.
Markers of cardiovascular risk in PHPT

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Table 3

Linear regression analyses with change in LDL-C as dependent variable.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Unadjusted estimates</th>
<th>Adjusted estimates (model summary: $R^2 = 0.294$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>Un-standardized $\beta$</td>
</tr>
<tr>
<td>Randomization (OBS/PTX)</td>
<td>0.047</td>
<td>0.415</td>
</tr>
<tr>
<td>LDL-C at baseline</td>
<td>0.235</td>
<td>-0.448</td>
</tr>
<tr>
<td>Statins started in study period</td>
<td>0.096</td>
<td>-1.131</td>
</tr>
</tbody>
</table>

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found. Unfortunately, the analyses of cholesterol and other metabolic parameters were limited to patients with available frozen blood samples. Although there was a large overlap between the 2- and 5-year cohorts, the present cohort was smaller than in the previously published 2-year results. In analyses restricted to patients with complete biochemical datasets at all three time points (0, 2 and 5 years; Total-C and LDL-C), we observed a difference between groups already after 2 years ($P<0.05$). The power to detect minor changes in parameters assessed in this study was limited (Table 2). Further, there were more patients starting with statins in the OBS group. Thus, we assume that the current results with an improvement of Total-C and LDL-C in the OBS group were caused by a combination of more OBS patients starting with statins, as discussed earlier, and a type 1 error caused by selection bias of patients included in the present cohort.

Taken together, we observed a positive effect of observation on LDL-C and Total-C in contrast to the hypothesized positive effect of PTX in patients with PHPT. However, differences in treatment with statins during the study and a potential bias in the analyzed cohort may have been confounding factors.

In conclusion, our results do not support that parathyroidectomy has positive metabolic effects on lipid and glucose metabolism and should not be a separate indication for surgery to modify cardiovascular risk factors in mild PHPT.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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