Patients with surgically cured primary hyperparathyroidism have a reduced quality of life compared with population-based healthy sex-, age-, and season-matched controls

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Abstract

Objective: Primary hyperparathyroidism (PHPT) is associated with feelings of fatigue and depression, as well as limitation to physical and mental functioning. These quality of life (QoL) characteristics improve after parathyroidectomy. However, whether former patients fully regain QoL compared with healthy controls is largely unknown.

Design and patients: Cross-sectional study. Fifty-one former PHPT patients, successfully treated by surgery (mean time since parathyroidectomy 7.4 (range 5–15) years), and 51 sex- and age-matched healthy controls.

Methods: The 36-item Short-Form Health Survey version 2 and the WHO-Five Well-being Index. The surveys included questions on overall physical and mental health, functioning, and limitation in daily life activities.

Results: Former patients scored significantly lower compared with controls in physical functioning ($P<0.01$), role limitation caused by emotional problems ($P<0.01$), vitality ($P<0.001$), and general health ($P<0.01$). Compared with the controls, cases had a lower median (interquartile range) score of physical component summary (PCS; 54.9 (47.9–58.7) vs 49.6 (45.2–55.9), $P=0.03$) and mental component summary (MCS; 55.4 (49.7–58.1) vs 52.5 (44.7–55.5), $P=0.04$). There was no association between time since operation and PCS or MCS. Compared with controls, cases had higher body mass index (BMI; 26.0 $\pm$ 4.7 vs 28.8 $\pm$ 6.0 kg/m², $P<0.001$) and a higher frequency of cardiovascular diseases (CVD; 41.2 vs 62.7%, $P=0.03$). After adjustment for differences in BMI and CVD, PCS did no longer differ between groups. However, adjustments did not change the finding of a lower MCS in cases compared with controls.

Conclusion: Even though QoL may improve substantially after surgery, former PHPT patients still have reduced QoL compared with healthy controls.

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Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder with a rising incidence by age. The disease is characterized by an inappropriately high secretion of parathyroid hormone (PTH) from one or more of the parathyroid glands, causing elevated plasma calcium levels. After plasma calcium was included in routine analyses, patients with PHPT are now often diagnosed by chance prior to development of symptoms and signs caused by PHPT, including osteoporosis, muscle fatigue, cardiovascular complications, renal stones, neuropsychiatric symptoms, and a reduced quality of life (QoL) (1–4). In response to surgical cure, overall improvements occur in QoL (5–9).

A reduced QoL and neuropsychological impairment in PHPT is well described using 36-item Short Form Health Survey (SF36) and specific neuropsychological tests, demonstrating a significant improvement following successful treatment (5–10). Whether these improvements correspond to healthy people has, for the neuropsychological part, been investigated by Joborn et al. (11) and Walker et al. (10). Both studies showed that after surgical cure, neuropsychological and cognitive features were similar to healthy controls. Neurovascular regain was further investigated by Mjaland et al. (12) using single-photon emission-computed tomography in order to investigate cerebral blood flow and metabolism in neuropsychiatry illness. The study demonstrated pathologically reduced cerebral blood flow in patients with untreated PHPT, which improved to normal following parathyroidectomy in 13 of 14 patients. However, whether QoL is also fully regained and comparable to healthy controls following surgical cure still needs to be investigated.
Therefore, in a cross-sectional study, we compared former PHPT patients with at least 5 years of recovery following surgery with population-based age- and sex-matched controls to explore whether QoL is fully regained following parathyroidectomy.

**Subjects and methods**

In a cross-sectional study, we compared 51 former PHPT patients with 51 sex-, age-, and season-matched population-based controls recruited from the general background population (Fig. 1). We identified 120 patients (aged 33–77 years) treated for PHPT between 1996 and 2004 at our hospital through regional file extraction of diagnosis. The inclusions criteria were as follows: i) preoperative hypercalcemia with elevated albumin-adjusted plasma calcium levels (mean of three consecutive measurements), ii) high normal (upper one-third of the reference range) or elevated plasma intact PTH levels (mean of two consecutive measurements > 5 pmol/l) (13, 14), and iii) persistent normocalcemia following surgery. All patients had a calcium creatinine clearance ratio > 0.01.

Exclusion criteria for both former patients and controls included individuals with metabolic bone disease other than PHPT, current malignancy, renal insufficiency, malabsorption (including gastric and intestinal resection), sarcoidosis, treatment with pharmacological doses of vitamin D and calcium, alcohol abuse, and recurrence or presence of PHPT (elevated plasma calcium levels and plasma PTH > 5.0 pmol/l).

**Participants**

We recruited the controls through direct mailings to a random sample from the general background population. Using the Danish Civil Registration System, a random list of male and female controls born from 1918 to 1990 and living in the area of our University Hospital was retrieved. For each included former patient, an invitation letter was send to age- (±2 years) and gender-matched control subjects.

Ninety-one former patients (aged 33–77 years, 81% women) answered the invitation among which 80 responded positively. Twelve patients did not fulfill the study criteria and were excluded. Of the 68 potential participants, 60 were selected at random. Approximately 600 controls were invited by letter; of them 399 responded to the invitation (aged 32–76 years, 84% women), 243 positively. Subsequently, 60 subjects who best matched the former patients were chosen. Two controls and two former patients dropped out excluding their matched participant. Additionally, two controls were excluded due to accidental undiagnosed PHPT and three were excluded due to recurrence of PHPT or secondary HPT among cases. In total, 51 matched cases and controls participated in the study.

All visits were conducted from start of February to end of March 2009. Matched cases and controls participated in the study within 2 weeks of each other.

Each participant gave informed consent, and the study was conducted according to the Declaration of Helsinki II. The Danish Data Protection Agency was notified about the study (#2008-41-2564), and the study was approved by The Central Denmark Region Committees on Biomedical Research Ethics (#M-20080159).

**Biochemical measurements**

Plasma levels of calcium, ionized calcium, TSH, phosphate, creatinine, albumin, and the renal excretions of calcium and creatinine were determined by standard methods on an automated chemistry analyzer (Hitachi 917, Roche). Plasma total calcium was corrected for individual variations in plasma albumin according to the equation: adjusted plasma calcium (mmol/l) = 1.14 × (0.700 – plasma albumin (mmol/l)) + plasma calcium, total (mmol/l).

Creatinine clearance was estimated by the Cockcroft and Gault formula (15). Plasma 25-hydroxyvitamin D (25OHD) levels were analyzed by isotope dilution liquid chromatography–tandem mass spectrometry by a method adapted from Maunsell et al. (16). Mean coefficients of variation (CV) for 25OHD3 were 6.4 and 9.1% at levels of 66.5 and 21.1 nmol/l, respectively, and for 25OHD2 the CV values were 8.8 and 9.4% at levels of 41.2 and 25.3 nmol/l respectively (17). Plasma intact PTH was measured using an automated immunoassay on the Cobas 6000 analyzer from Roche.
The lower limit of detection was 0.127 pmol/l. The intra-assay precision was 3.69 pmol/l, CV = 3.3% and 26.6 pmol/l, CV = 2.7%.

Quality of life

We used the Danish version 2 of the SF36. The health survey is highly validated and received favorable evaluation by independent rating (18). It comprises 36 questions grouped into eight health concepts (physical functioning, role limitation caused by physical problems, bodily pain, general health perception, vitality, social functioning, role limitation caused by emotional problems, and mental health), which together form a mental component summary (MCS) and physical component summary (PCS). The eight subscales are linearly transformed from 0 to 100. MCS and PCS are calculated on norm-based estimates of a general population and set to have a mean of 50 and an s.d. of 10.

WHO-Five Well-being Index (19) comprises five 6-point-rated questions with a theoretical raw score ranging from 0 to 25. The points are transformed into a scale from 0 (worst thinkable well-being) to 100 (best thinkable well-being), thus higher scores mean better well-being.

Finally, the participants completed a questionnaire on general well-being and illnesses (Table 1). The questionnaire included questions on whether the participants had been diagnosed with diseases known to be

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of studied subjects. Values are presented as n(%), mean ± s.d., or median (25–75% interquartile range).</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Controls</td>
</tr>
<tr>
<td>Age (years; range)</td>
<td>61 (36–77)</td>
</tr>
<tr>
<td>Females (n, %)</td>
<td>90 (88.2)</td>
</tr>
<tr>
<td>Time since surgery (years; range)</td>
<td>7.4 (5–15)</td>
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<tr>
<td>Body mass index (kg/m²; mean ± s.d.)</td>
<td>26.0 ± 4.7</td>
</tr>
<tr>
<td>Life style characteristics</td>
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<td>User of vitamin D supplements (n, %)</td>
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<tr>
<td>Use of calcium supplement (n, %)</td>
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<tr>
<td>Dietary calcium intake (mg/day)²</td>
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<tr>
<td>Total calcium intake (mg/day)²</td>
<td>1050 (800–1400)</td>
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<tr>
<td>Alcohol intake</td>
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<tr>
<td>Never drinking (n, %)</td>
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<tr>
<td>Drink (n, %)</td>
<td>40 (96.1)</td>
</tr>
<tr>
<td>Smoking</td>
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</tr>
<tr>
<td>Non-smoker (n, %)</td>
<td>24 (47.1)</td>
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<tr>
<td>Former smoker (n, %)</td>
<td>19 (37.3)</td>
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<tr>
<td>Current smoker (n, %)</td>
<td>8 (15.6)</td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
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<tr>
<td>P-PTH (pmol/l; mean ± s.d.)</td>
<td>4.8 ± 1.4</td>
</tr>
<tr>
<td>P-PTH adj (pmol/l)²</td>
<td>5.12 (4.65–5.59)</td>
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<tr>
<td>P-calcium total (mmol/l; mean ± s.d.)</td>
<td>2.36 ± 0.09</td>
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<tr>
<td>P-calcium, albumin adj (mmol; mean ± s.d.)</td>
<td>2.37 ± 0.09</td>
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<tr>
<td>P-phosphate (mmol/l; mean ± s.d.)</td>
<td>1.02 ± 0.17</td>
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<td>P-TSH (mU/l)²</td>
<td>1.67 (1.13–2.36)</td>
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<tr>
<td>P-creatinine (µmol/l; mean ± s.d.)</td>
<td>70.63 ± 14.29</td>
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<td>P-creatinine clearance (ml/min)²</td>
<td>86.3 (76.4–99.3)</td>
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<td>P-25OHD (nmol/l; mean ± s.d.)</td>
<td>55.7 ± 21.8</td>
</tr>
<tr>
<td>P-25OHD adj (nmol/l)²</td>
<td>56.3 (50.2–62.3)</td>
</tr>
<tr>
<td>Feeling of muscle fatigue (n, %)</td>
<td>15 (29.4)</td>
</tr>
<tr>
<td>Feeling of pain (n, %)</td>
<td>29 (56.9)</td>
</tr>
<tr>
<td>Stair walking without support (n, %)</td>
<td>44 (86.7)</td>
</tr>
<tr>
<td>Rising from chair without support (n, %)</td>
<td>49 (96.1)</td>
</tr>
<tr>
<td>Diagnosed with hypertension (n, %)</td>
<td>13 (25.5)</td>
</tr>
<tr>
<td>Ischemic heart disease (n, %)</td>
<td>10 (19.6)</td>
</tr>
<tr>
<td>Operation on the heart (n, %)</td>
<td>2 (3.9)</td>
</tr>
<tr>
<td>Other heart diseases (n, %)</td>
<td>3 (5.9)</td>
</tr>
<tr>
<td>Cardiovascular diseases (n, %)</td>
<td>21 (41.2)</td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td>2 (3.9)</td>
</tr>
<tr>
<td>Renal impairment (n, %)</td>
<td>--</td>
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<tr>
<td>Pancreatitis (n, %)</td>
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</tbody>
</table>

²Median with interquartile range (25–75% percentiles).

²Dietary + supplement calcium intake (mg/day).

²Adjusted for sex, age, scaled body weight, creatinine, and 25OHD (95% CI).

²Adjusted for BMI (95% CI).

The term ‘cardiovascular disease’ was used when a subject answered positively to at least one of the questions on hypertension, ischemic heart disease, previous operation on the heart, or other heart diseases.
associated with PHPT including hypertension, cardiovascular diseases (CVD), renal impairment, diabetes, and pancreatitis (Table 1). Weighing scales were used to measure body weight (BW) in light indoor clothes and height was measured without shoes using a stadiometer. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m²).

**Statistical analysis**

Assuming a mean MCS or PCS of 50, with an s.d. of 10, 43 subjects were needed in each group in order to detect a between-group difference in scores equal to 7, with 90% statistical power at a 5% level of significance. We assessed the differences between groups using $\chi^2$ test for categorical variables and two-sample $t$-test or Mann–Whitney $U$ test for continuous variables, as appropriate, after testing for normal distributions. Correlations between variables were assessed by Spearman’s rho. Using a general univariate linear model, we adjusted for differences between groups. Results are reported as mean ± S.D. or as median with interquartile range (IQR; i.e. the 25 and 75% percentile). We performed the statistical analysis using the Statistical Package for Social Sciences (SPSS 14.0, Chicago, IL, USA) for Windows.

**Results**

In total 102 persons were included in the analyses divided into 51 former PHPT patients and 51 controls. Cases and controls were well matched with a mean age of 61 (range 36–77) years (Table 1). In each group, 45 (88%) were females. Mean time from diagnosis till parathyroidectomy was 6.9 (range 0–37) months.

Of the cases, 41 had pathological verified adenoma, three had hyperplasia, and three had unclassified parathyroid pathology, whereas the histopathological data from four patients could not be retrieved.

Former patients and controls did not differ in terms of lifestyle characteristics, including use of vitamin D and calcium supplements, daily calcium intake, alcohol intake, and smoking (Table 1). Moreover, biochemical indices were similar between groups including plasma levels of calcium, creatinine, PTH, TSH, and 25OHD.

For the entire study population, mean BMI was 27.3 (range 18.7–51.0) kg/m². A similar number of former patients ($n=29$: 57%) and controls ($n=27$: 53%) had overweight (BMI 25–30 kg/m²). However, obesity (BMI > 30 kg/m²) was more common in the group of former patients ($n=14$: 28%) than in the controls ($n=6$: 12%, $P=0.046$).

Stratification by sex showed that compared with the controls, former female patients had a significantly higher BW (72.2 ± 12.8 vs 79.5 ± 19.2 kg, $P=0.03$) and BMI (26.0 ± 4.7 vs 28.8 ± 6.0 kg/m², $P<0.01$). Moreover, within the group of former female patients, BW and BMI were significantly higher at the time of this study compared with values at the time of diagnosis, whereas anthropometric indices did not differ between groups in males (Fig. 2).

Compared with the controls, former patients complained more frequently of a feeling of muscle fatigue ($P<0.03$) and unspecified pain ($P<0.02$; Table 1). Finally, a diagnosis of hypertension and CVD was more frequent in former PHPT patients than in the controls ($P<0.01$ and $P=0.03$ respectively). A diagnosis of CVD, however, was not more common in the group of participants with BMI > 25 compared with BMI < 25 kg/m² ($P=0.77$).

**Quality of life**

As shown in Table 2, former PHPT patients scored significantly lower compared with controls in physical functioning ($P=0.01$), role limitation caused by emotional problems ($P=0.01$), vitality ($P<0.001$), and general health ($P=0.01$). The PCS score was significantly ($P=0.03$) lower in former patients (49.6 (45.2–55.9); median IQR with 25–75 percentiles) compared with the controls (54.9 (47.9–58.7)). Also, MCS was lower among cases (52.5 (44.7–55.5)) than in the controls (55.4 (49.7–58.1), $P=0.04$). When adjusting for CVD, there were no significant differences between cases and controls in PCS (50.25 (48.03–52.47) vs 51.88 (49.66–54.10), $P=0.31$) or physical functioning (49.42 (47.37–51.47) vs 51.85 (49.66–54.10), $P=0.10$).

In the overall study population (combining cases and controls), there was a significant inverse correlation between PCS and BMI (Fig. 3). After adjustment for differences in BMI, as well as for differences in BMI, age, and CVD, PCS adj. did no longer differ between groups (51.15 (49.09–53.21) vs 50.98 (48.92–53.04),
However, no association was present between BMI and MCS neither overall nor in each subgroup (Fig. 3), and MCS remained significantly lower among cases after adjustment for BMI, age, and CVD (53.46 (51.18–55.75) vs 50.06 (47.77–52.34), P<0.04). Time since operation and QoL did not correlate – neither did QoL and time from diagnosis till operation (data not shown). WHO-Five Well-being Index did not differ between groups (Table 2).

### Discussion

Our study showed a significantly reduced QoL as well as a higher BMI and a higher frequency of CVD in former PHPT patients compared with age- and sex-matched controls recruited from the general background population. However, when adjusting for CVD, PCS and physical functioning were practically identical for the two groups, but MCS remained significantly lower in cases compared with controls despite adjustments.

To the best of our knowledge, this study has the longest ‘follow-up time’ after parathyroidectomy (mean 7.4 years) on effects of PHPT on QoL.

Reduced QoL including weakness, mood swings, and feeling of malaise are well-known symptoms among patients with PHPT, and several studies have documented a low QoL score as assessed by the SF36 in patients prior to surgery (5–7, 20, 21). A reduced QoL has also been reported in subjects with mild PHPT, normally considered asymptomatic (22). Beneficial effects of surgery on QoL have been shown by several investigators, as assessed by the SF36 questionnaire, visual analogue scales or other symptom-specific questionnaire-based assessment tools (5–9, 20, 21). This is also supported by two randomized controlled studies showing a modest improvement in QoL in patients treated with surgery compared with medical observation (22, 23). However, only scarce data are available on whether QoL is fully regained following normalization of plasma calcium and PTH levels. In the study by Bollerslev et al. (22), psychological symptoms as assessed by the Comprehensive Psychopathological Rating Scale (CPRS) improved only slightly following surgery. Nevertheless, 2 years after parathyroidectomy, the patient group had significantly more symptoms than a cohort of healthy controls, indicating that symptoms lasted beyond surgical cure. Similarly, although physical functioning is known to improve following surgery, only few studies with discrepant
results have reported whether physical functioning is fully regained. In a group of 74 patients with PHPT, Sheldon et al. (7) reported a full regain of QoL 1 year following surgical cure with no difference between former patients and the age-matched national norm in any of the measured eight specific SF36 health domains. Moreover, using a disease-specific outcome questionnaire designed specifically for PHPT, Pasieka et al. (8) reported a significant improvement following surgery with no difference 1 year following surgery between former PHPT patients and thyroidectomized non-toxic thyroid patients. Nevertheless, using another group of patients as controls may cause bias, as these controls also have a disease that may impair their QoL (24, 25). In contrast, compared with norm-based population data, two studies have reported a sustained impaired QoL in terms of physical function (5, 7). In a group of 59 patients with PHPT, Burney et al. (5) reported a significantly improved QoL 6 months following parathyroidectomy compared with pre-surgery. However, despite improvements in the mean physical function SF36 scale, the score was still below the population-based norm 6 months following surgery. Likewise, 15 months following parathyroidectomy, Sheldon et al. (7) reported QoL parameters equal to norm based except for physical functioning, which was significantly lower in the group of 72 patients. Our study had a substantial longer follow-up time than any of the previous studies, showing a sustained impairment of QoL in terms of both mental health and physical functioning compared with population-based controls matched on sex, age, and season.

Although the difference in the SF36 score between the group of patients considered here and controls may seem small, it may be of clinical importance. On an average, former PHPT was associated with a six-point lower vitality score, which is of similar magnitude as the decrease in vitality score reported in patients with congestive heart failure (−5.8 points), anemia (−5.4 points), and chronic obstructive lung disease (−5.7 points), but of a lower magnitude than in patients with clinical depression (−13 points) (26). In the Medical Outcomes Study (MOS), a five-point lower vitality score was associated with a significantly increased risk of job loss (hazard ratio (HR) 1.15; 95% confidence interval (CI) 1.09–1.21) and hospitalization (HR 1.09; 95% CI 1.05–1.12) (26).

The impaired QoL may be influenced by the fact that former patients had a higher BMI compared with controls. In this study, BMI was correlated to PCS both in the overall study population and in the groups and when adjusting for BMI PCSadj, no longer differed from controls. There is a well-known association between PHPT and increased BW (27). The underlying mechanisms are unknown to date, although a study by Grey et al. (28) has suggested that adiposity may predispose to PHPT.

The fact that female former patients actually gained in weight may be explained by the menopause-associated weight gain (29) as none of the male patients gained any weight (30). Previous studies have also demonstrated an inverse association between obesity and reduced QoL (31–33). Jones et al. (31) reported decreased physical functioning, vitality, and general health perception in obese postmenopausal women. These indices were also significantly reduced in our former patients. However, our data do not allow us to draw final conclusions on whether a feeling of physical and mental impairment causes a reduced activity level resulting in overweight or whether adiposity is the reason for impaired QoL. To further evaluate the impact of BMI in relation to QoL in former PHPT, it would be of interest to investigate whether BMI-, sex-, and age-matched controls scored differently in QoL.

In addition to obesity, the presence of comorbidities following PHPT may also explain the impaired QoL. An impaired QoL has been reported in patients with osteoporosis (34, 35), CVD (36), hypertension (37), and renal stone disease (38). As risk of these diseases is increased in PHPT, the impaired QoL may be due to such chronic diseases caused by PHPT. In fact, a diagnosis of hypertension and CVD was more frequent in former PHPT patients than in controls and when adjusted for, PCS no longer differed between groups. This may also explain the lack of correlation between time since parathyroidectomy and measured indices of QoL, i.e. if a chronic disease causing a reduced QoL is due to PHPT, this may cause a chronic impairment of QoL that does not wane in the years following surgical cure for PHPT. Finally, as suggested by Walker et al. (39), a sustained reduced QoL may be due to the burden, by itself, of having been diagnosed with a disease.

Strengths and limitations

There are several strengths in our study. Patient and control were carefully matched according to sex and age. Furthermore, former patient and matched control participated within 2 week of each other in February and March where sun exposure would not lead to changes in P-26OHD. The fact that former PHPT patients were compared with population-based healthy controls gives valid results regarding these patients’ incomplete regain of QoL following parathyroidectomy. Still, there are limitations including potential selection bias regarding cases if we are recruiting mainly those with physical complaints and, in controls, if we are predominantly including ‘super normal’ individuals, excluding the mentally and functionally impaired. However, for ethical reasons, we are not allowed to address those patients and controls who did not want to participate in the investigation.

At present, we do not feel that our study supports an altered policy regarding surgery versus no surgery in
‘asymptomatic’ PHPT (40). This decision depends on the long-term outcome of randomized trials evaluating the effect of surgery versus observation (22, 23, 41). More studies on patients with surgically cured PHPT are warranted, as it seems that past PHPT causes a chronic health impairment that is not fully cured by parathyroidectomy. Hence, future studies should address the question of whether increased BMI could be causally involved in the reduced QoL in these patients – either by matching for BMI or by intervention studies trying to reduce BW and BMI.

Conclusions

More than 5 years after surgical treatment for PHPT, former patients have a lower QoL and a higher BMI compared with healthy sex- and age-matched controls. The reduced QoL may in part be related to a higher BMI and a higher frequency of CVD in former patients, indicating the importance of measures to prevent the comorbidity related to 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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