Surgical Treatment of Hyperparathyroidism Improves Health-Related Quality of Life

David G. Sheldon, MD; Faye T. Lee, RN; Nancy J. Neil, PhD; John A. Ryan, Jr, MD

Hypothesis: The surgical treatment of primary hyperparathyroidism results in an improved health-related quality of life.

Design: Prospective cohort analysis of consecutive patients with primary hyperparathyroidism analyzed preoperatively and 1 year postoperatively.

Setting: Academic multispecialty referral clinic.

Patients: We prospectively evaluated 74 consecutive patients who underwent parathyroid exploration for primary hyperparathyroidism during a 15-month period.

Interventions: The Medical Outcomes Study Short-Form Health Survey (SF-36) was administered before consultation with a surgeon. Patients were categorized based on reason for referral as either asymptomatic (group 1; n=43) or symptomatic (group 2; n=29). All patients underwent parathyroid exploration and normalization of calcium levels postoperatively. The SF-36 was then re-administered after 1 year.

Main Outcome Measures: Statistical analysis of preoperative and postoperative SF-36 scores, and comparisons with national norms.

Results: The SF-36 was completed preoperatively and 1 year postoperatively by 72 (97%) of 74 patients. When the results were compared with published national norms, the preoperative population was significantly impaired in 5 of 8 domains, whereas the postoperative one had improved and was nearly indistinguishable from the norm. In 7 of 8 domains, the postoperative scores were significantly improved compared with preoperative scores. Group 1 patients showed significant preoperative impairment in 3 domains and significantly improved in 2, whereas group 2 patients showed significant impairment and improvement in 7 domains.

Conclusion: The surgical treatment of primary hyperparathyroidism is associated with durable, statistically significant improvements in health-related quality of life.

Arch Surg. 2002;137:1022-1028
Patients' functional status and compare quality of life with national norms.

**Patients and Methods**

Seventy-four consecutive patients who were referred to a single surgeon for primary hyperparathyroidism were prospectively studied during a 13-month period. No patient with the diagnosis of primary hyperparathyroidism was excluded. Prior to an initial surgical consultation, informed consent was obtained for study purposes, and patients completed the SF-36. The SF-36 is designed to assess overall functional status and well-being for adult patients compared with age-matched US population norms. The form has 36 questions that assess 8 specific health domains: general health perception, physical function, social function, role limitations attributed to physical problems, role limitations attributed to social problems, bodily pain, mental health, and energy/fatigue. This instrument was selected because it is practical, well suited for clinical use, and inexpensive and has been validated in a variety of disease conditions in adults, including primary hyperparathyroidism.11,16

A medical history, physical examination, and appropriate serum and/or urine chemistry values confirmed primary hyperparathyroidism in all patients. All of them underwent preoperative localization studies similar to our previously described protocol.17 Patients were categorized into 2 groups based on the characterization of their hyperparathyroidism by their referring physician. Group 1 patients were thought to be without symptoms attributable to this condition. We labeled this group “asymptomatic.” Group 2 patients were referred by their physician for classic symptoms of hyperparathyroidism. We labeled this group “symptomatic.”

<table>
<thead>
<tr>
<th>Table 1. Primary Reason for Referral to a Surgeon*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Patients</strong></td>
</tr>
<tr>
<td>Group 1: asymptomatic (n = 43)</td>
</tr>
<tr>
<td>Abnormal DEXA scan result</td>
</tr>
<tr>
<td>Persistent hypercalcemia</td>
</tr>
<tr>
<td>Young age (&lt;50 y)</td>
</tr>
<tr>
<td>Group 2: symptomatic (n = 29)</td>
</tr>
<tr>
<td>Nephro lithiasis</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Mental status changes</td>
</tr>
<tr>
<td>Life-threatening hypercalcemia</td>
</tr>
<tr>
<td>Fracture</td>
</tr>
<tr>
<td>Thirst and polyuria</td>
</tr>
</tbody>
</table>

*Some patients had multiple reasons for referral. The table lists what the referring physician perceived was the primary indication for parathyroidectomy. DEXA indicates dual-energy x-ray absorptiometry.

Parathyroid exploration was then performed in all patients. Type of operative procedure, pathologic results, postoperative morbidity, length of hospital stay, and postoperative serum calcium levels were recorded. One year following the procedure, a second SF-36 questionnaire was mailed to the patient and returned for analysis. Preoperative and postoperative responses were pooled and compared with age-matched national norms. In each domain of the SF-36, we established a 95% confidence interval (±1.96 SEM) based on the scale score for the norm. Statistical significance was defined as a pooled patient score falling outside of the 95% confidence interval in each domain.11,16 Quantitative analysis of each patient's preoperative and postoperative SF-36 responses was accomplished using paired comparisons with the Wilcoxon rank sum test.

**Results**

The study population included 72 (97%) of 74 patients who completed both the preoperative and postoperative SF-36 questionnaires. Group 1 (asymptomatic) had 43 patients, and group 2 (symptomatic) had 29 patients. The total population consisted of 21 men and 51 women, with a mean age of 61 years. The type of procedure performed was 4-gland exploration in 27 patients (37%), unilateral neck exploration in 38 patients (53%), and minimally invasive 1-gland exploration in 7 patients (10%). No perioperative complications occurred, and all patients were discharged from the hospital either on the day of their operation or the next morning. The pathologic findings were as follows: 66 solitary adenomas (92%), 4 double adenomas (6%), 1 case of 4-gland hyperplasia (1%), and 1 case of 5-gland hyperplasia (1%). Postoperative serum calcium levels were normalized in 73 (99%) of 74 patients. One patient required a second procedure after unilateral neck exploration to remove an unexpected contralateral adenoma.

The reasons for referral to the surgeon are outlined in Table 1. The most common reason for referral was osteoporosis as indicated by an abnormal result on a dual-energy x-ray absorptiometry (DEXA) scan (32/43, or 74% of the patients in group 1).

Compared with age-matched national norms, the preoperative study population demonstrated significant impairment in functional health in 5 of 8 domains of the SF-36: physical function, physical role limitations, social function, bodily pain, and energy/fatigue (Table 2). Postoperatively, however, the study population improved and

<table>
<thead>
<tr>
<th>Table 2. SF-36 Data for All Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Domain</strong></td>
</tr>
<tr>
<td>General health perception</td>
</tr>
<tr>
<td>Physical function</td>
</tr>
<tr>
<td>Role limitation (physical)</td>
</tr>
<tr>
<td>Role limitation (emotional)</td>
</tr>
<tr>
<td>Social function</td>
</tr>
<tr>
<td>Bodily pain</td>
</tr>
<tr>
<td>Mental health</td>
</tr>
<tr>
<td>Energy/fatigue</td>
</tr>
</tbody>
</table>

*Mean preoperative and postoperative scores highlighted in boldface reached significance at P<.05 compared with national norms. Scores for all patients (N = 72) were measured on a scale of 0 to 100. SF-36 indicates Medical Outcomes Study Short-Form Health Survey.
was nearly indistinguishable from the age-matched norms for the general US population. Table 3 demonstrates that group 1 (asymptomatic) was significantly impaired preoperatively compared with national norms in 3 domains: physical function, physical role limitations, and energy/fatigue. Table 4 demonstrates that group 2 (symptomatic) was significantly impaired preoperatively compared with national norms in 7 of 8 domains: general health perception, physical function, physical role limitations, social function, bodily pain, mental health, and energy/fatigue.

Table 5 outlines the statistical differences between the postoperative study population and the preoperative study population. There was significant improvement in 7 of 8 domains of the SF-36 after parathyroidectomy. Table 5 also demonstrates that the asymptomatic population (group 1) improved significantly in 2 domains: mental health and energy/fatigue. Group 2 (symptomatic) significantly improved in 7 of 8 domains.

**COMMENT**

In our consecutive series of patients with primary hyperparathyroidism, parathyroidectomy improved health-related quality of life. This finding was consistent whether patients were classified as symptomatic or asymptomatic. Notably, patients characterized by their referring physician as asymptomatic were impaired preoperatively and demonstrated improvement after parathyroidectomy. Our results affirm the argument that few people referred for primary hyperparathyroidism are truly without symptoms.16,19-22
The NIH panel recommended operative intervention in the asymptomatic patient with any of the following factors: markedly elevated serum calcium level, a previous episode of life-threatening hypercalcemia, reduced creatinine clearance, asymptomatic kidney stones, elevated 24-hour urinary calcium excretion, age younger than 50 years, or substantially reduced bone mass. Because the consensus conference did not address health-related quality of life in primary hyperparathyroidism, its recommendations may not treat a patient population with impaired physical or emotional function and fatigue. Our results imply that an evaluation of health-related quality of life may be helpful in the assessment of patients with hyperparathyroidism.

The gains in perceived health status were even more pronounced in the symptomatic group, with the data reaching statistical significance in nearly all domains of the SF-36. This group was more impaired preoperatively and made greater gains in health status after parathyroidectomy. Our findings rely on patient-reported symptoms, and this method is inherently subject to bias. Bias was minimized in several ways. First, no patient with primary hyperparathyroidism was excluded from the prospective study. Previous studies of symptom evaluation in primary hyperparathyroidism have used selected populations or those in which many potential subjects refused to participate.11,16,21,23 Second, our postoperative evaluation was comprehensive. Based on 97% of consecutive patients responding at 1 year, our data are among the most complete reported in the literature with regard to parathyroid surgery. Third, we minimized the potential for a surgeon’s bias to influence the patient’s health perception by administering the SF-36 prior to consultation. Similarly, patients completed the follow-up SF-36 by mail so that they did not have to visit the surgeon’s office to respond. Fourth, reevaluation 1 year after the procedure limits interventional bias, or the phenomenon of patients responding at 1 year, our data are among the most complete reported in the literature with regard to parathyroid surgery. Additionally, our data demonstrate that patients with primary hyperparathyroidism demonstrated statistically significant improvement regarding preoperative quality of life as measured with the SF-36. Parathyroidectomy significantly improved quality of life, and the effect is durable at 1 year. Most notable are the findings that patients thought to be asymptomatic by the referring physician were preoperatively impaired and that they made improvements in mental health and energy/fatigue levels after parathyroidectomy.

Presented at the 73rd Annual Meeting of the Pacific Coast Surgical Association, Las Vegas, Nev, February 17, 2002. The discussions are based on the originally submitted manuscript and not the revised manuscript.

Corresponding author: John A. Ryan, Jr, MD, Section of General, Vascular, and Thoracic Surgery, Virginia Mason Medical Center, PO Box 900 C6-GSUR, 1100 Ninth Ave, Seattle, WA 98111 (e-mail: gtsjar@vmmc.org).

REFERENCES

13. McHorney CA, Ware JE Jr. Construction and validation of an alternate form gen-
eral mental health scale for the Medical Outcomes Study Short-Form 36-Item Health Survey, Med Care. 1995;33:15-28.


DISCUSSION

Quan-Yang Duh, MD, San Francisco, Calif: Six years ago, Richard Burney of Michigan presented at the American Association of Endocrine Surgeons meeting in Napa Valley, Calif. He was the first to use the SF-36 to show an improved health-related quality of life in patients with primary hyperparathyroidism after parathyroidectomy. At that time, Dr Burney showed that patients with primary hyperparathyroidism had impaired health-related quality of life as measured by the SF-36. Six months after parathyroidectomy, 7 of 8 domains in the SF-36 improved by 10 or more points, and the scores became the same as those for the normal controls. Several more studies since then have confirmed these findings. Some skeptics, however, are still not convinced; they are concerned that the selection bias produced by the randomization of patients and the use of controls could introduce bias; that is, those whose quality of life has improved may be more likely to complete the survey.

Dr Sheldon and colleagues addressed this question of patient selection by both including consecutive patients and having a near-perfect survey response. Those of you who have tried to perform surveys know that this is extremely difficult. This paper convincingly demonstrated that this improvement in quality of life is real, and not just an artifact of patient selection.

Once the benefit of parathyroidectomy was demonstrated, a second aspect of this paper was to stratify the patients to determine whether some groups may benefit more and others may not. The authors stratified these patients into an “asymptomatic” group and a “symptomatic” group and found that both groups improved in their SF-36 scores 1 year after parathyroidectomy, although the improvement was more significant in the symptomatic group. This stratification seems to help us predict the expected improvement from parathyroidectomy by preoperative symptoms.

Since the NIH consensus conference of 1991, there has been a sea change in the field of surgery for the parathyroid. First of all, more unilateral exploration and focused exploration are now done, with results as good as the traditional operation. This was made possible by improved preoperative localization studies, especially sestamibi scan, and intraoperative quick PTH [parathyroid hormone] assay. In addition, our study and others have shown that patients benefit from parathyroidectomy even if they do not fit the so-called NIH criteria. What we have learned over the past 10 years is that (1) parathyroidectomy can be performed safely with less invasiveness, and (2) more patients, especially those with milder disease, can benefit from parathyroidectomy. Dr Sheldon’s paper supports this growing opinion among the endocrine surgeons. We all hope that when the NIH revisits this issue in the consensus conference this April, 2 months from now, it will liberalize the indications for parathyroidectomy in patients with less severe primary hyperparathyroidism.

I have 2 questions for the authors: (1) Since control group is always an issue, and a randomized study has not yet been done, have you studied a surrogate control group (for example, patients with primary hyperparathyroidism who may have delayed or declined their operations, or patients who have had a thyroidectomy)? (2) Since stratifying patients as “symptomatic” or “asymptomatic,” as you have noted, is not precise, have you also stratified the patients differently (for example, either by whether or not they fit the NIH criteria for parathyroidectomy or by the severity of their biochemical abnormalities, such as the calcium or PTH levels)?

It is good to know that parathyroidectomy not only prevents morbidity and premature death associated with hyperparathyroidism but also improves the quality of life and makes the patient feel better.

John A. Butler, MD, Orange, Calif: The major question addressed by this paper concerns the asymptomatic group. What you showed is that preoperatively they were significantly impaired in 3 of the 8 categories. Postoperatively they improved in 2 of 8, but it was actually only in 1 of the 3 that they were preoperatively impaired. In the other category in which they significantly improved, they were actually better than the norm in the preoperative assessment. Whereas I agree with your bias, I just wonder how strongly you feel your data support your conclusions, particularly in that asymptomatic group.

Michael J. Hart, MD, Seattle, Wash: My question is similar to Dr Butler’s and has to do with your survey instrument. I assume, and please let me know if this is true, that there has been validation of the SF-36 health questionnaire by using it on the same population over a number of different years to determine the variability in responses. Likewise, the things that you mention most frequently—mental health, fatigue, energy levels—are probably the most nebulous and hardest areas to measure. I’m not sure that if I took that test from year to year I would be all that consistent, or even from day to day. I would like for you to give us a little bit more background about the SF-36 questionnaire and its referencing.

Orlo H. Clark, MD, San Francisco: I congratulate Dr Sheldon and colleagues on this excellent paper. They address a currently controversial issue; that is, do “asymptomatic” and “symptoms”
tomatic” patients benefit symptomatically from successful parathyroidectomy?

Most investigations suggest that about 75% to 80% of patients improve following parathyroidectomy. This means that 20% to 25% do not. We have studied whether patients who fit and who did not fit the NIH criteria for parathyroidectomy receive the same psychological improvement after successful parathyroidectomy. We found that both groups benefit.

My first question is, did you study the duration of symptoms prior to parathyroidectomy and whether patients who had symptoms for a shorter time preoperatively were more likely to benefit symptomatically? Second, were there any other factors that might help predict whether a patient would improve symptomatically, such as PTH level, calcium level, patient age, or symptom complex? Although other investigations using SF-36 testing support your findings, including those of Burney, Pasieka, Talpos, and colleagues, I believe your new findings not only confirm their studies but also document that the symptomatic benefit of parathyroidectomy continues for at least 1 year.

Julie A. Freischlag, MD, Los Angeles, Calif: We administer the SF-36 in our clinic every time a patient comes to visit us. Part of that is for entertainment while they wait in the lobby, but it is also for scientific purposes. Our group of patients that we really worry about are TOS [thoracic outlet syndrome] patients, and we are trying to do a study looking at the SF-36 to see if we really help them. One of the specialists told us, you need to give this survey to your patients and then ask them if there is something you missed, or should you have asked them if something was really bothering them, to know whether this general survey reflects their true improvement. My question to you is, did you ask them about symptoms or feelings that perhaps an instrument may have missed that they would have liked to be asked about?

Philip D. Schneider, MD, Sacramento, Calif: It’s the closest approximation to the aborted Mayo Clinic trial that was started in the 1960s studying asymptomatic hypercalcemic patients. It really gets at the issue of what may happen to patients who do not have surgery. I have a couple of questions.

There were a large number of patients who were referred with abnormal DEXA scans, and I am curious whether they were referred only because the DEXA scan was abnormal and they were known to be hypercalcemic, or whether because they were about to go on hormone replacement therapy, they had a DEXA scan and it had not been appreciated that they were hypercalcemic. Finally, I would be curious if you administered the SF-36 to patients who came to your clinic and then refused surgery, and then had the opportunity to do long-term follow-up on those patients to see if their condition deteriorated.

Lawrence Way, MD, San Francisco: I would like to expand on previous comments concerning the possibility of bias. Cognitive psychologists report that people’s “mood” influences a variety of subjective assessments, such as those contained in the quality-of-life grid (Psych Res. 1999;88:173). Before their first quality-of-life assessment, the patients in this study, although asymptomatic, would have been told that they had hyperparathyroidism and had probably received conflicting opinions on the significance of the disease and the importance of treatment. The resulting confusion could well have affected their mood and hence their quality-of-life assessments. Since all of this uncertainty would have been relieved by the operation, reported improvement in quality of life might have stemmed, at least in part, from these uncontrolled psychological factors.

Dr Ryan: I appreciate the interest in this paper and Dr Quan-Yang Duh’s excellent discussion. I will try to answer the questions that were asked, and then I have a short video to show you.

Dr Duh asked 3 questions. Did we have a control group of patients not operated on but followed up with the SF-36? No, but Dr Talpos from Henry Ford Hospital has published a randomized trial of patients with mild hyperparathyroidism either operated on or observed showing a benefit in the operative group as judged by the SF-36 (Talpos GB, Bone HG, Kleerekoper M, et al. Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism: patient description and effects on the SF-36 health survey. Surgery. 2000;128:1013-1020).

Did we stratify the patients by the NIH criteria? No, in our 43 so-called asymptomatic patients, all but 8 of the patients met NIH criteria; most had been referred for abnormal bone marrow density (32), and there were 3 patients less than 50 years of age. However, Drs Burney and Thompson at the University of Michigan did stratify patients by high and low calcium elevations and demonstrated both impairment and postoperative improvement by SF-36 evaluation, independent of calcium level (Burney RE, Jones KR, Christy B, Thompson NW. Health status improvement after surgical correction of primary hyperparathyroidism in patients with high and low preoperative calcium levels. Surgery. 1999;125:608-614).

Dr Duh and others complimented the completeness of our long-term evaluation. We have a secret weapon at Virginia Mason, our coauthor and office nurse Faye Lee, RN, who somehow can find patients and get them to respond to long-term evaluations. These patients were referred from over a 5-state area. We realize the importance of having long-term evaluations, and we are fortunate to have someone who is extremely persistent in getting them done.

Dr Way, Hart, and Freischlag asked questions about the SF-36 survey. This was a questionnaire that was developed because the HCFA [Health Care Financing Administration] wanted to have a survey for health-related quality of life. The HCFA commissioned the Rand Corporation to form a Medical Outcome Trust to develop a questionnaire that could be used in a variety of situations and diseases. The SF-36 was published in 1992 (Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): 1. conceptual framework and item selection. Med Care. 1992;30:473-483).

No matter what group you are studying, the Medical Outcome Trust gives age- and sex-matched national norms for that group. Perfect health in any of the 8 domains of evaluation is given a score of 100. This questionnaire has been used widely in the last decade and, I believe, has become an accepted standard. Dr Thirby presented information to the PCSA [Pacific Coast Surgical Association] in 1998 about the SF-36 in Crohn disease.

Dr Clark asked about patients who did not improve postoperatively as judged by the SF-36. We did not specifically look at any individual patient, but rather the aggregate of our 72 patients. In fact, although I operated on every patient, I did not see any individual SF-36 results or have any personal involvement with administering the test. I hope this eliminated a form of bias.

Dr Schneider asked about the bone mineral density test. Thirty-two of the 43 so-called asymptomatic patients were referred to us because they had a low bone mineral density. For parathyroid surgeons, this test has been a boon. Physicians who are following patients with slightly elevated calcium levels and the diagnosis of hyperparathyroidism who don’t have kidney stones, broken bones, or pancreatitis (any of the traditional indications for referral) do note osteopenia or osteoporosis on a bone mineral density test and at that point feel an obligation to refer the patients to a surgeon.

Dr Butler asked 2 pertinent questions. How did we really stratify the patients into the asymptomatic group? The stratification was crucial to our study. We really wanted to see if the
patients sent as asymptomatic would improve postoperatively. When patients came to us, we read very carefully their referring notes by either an endocrinologist or primary care doctor, and we asked the patients their perception of why they were sent. If they said they were sent because of an abnormal laboratory value or an abnormal bone density test, then we classified them into the asymptomatic group. Although the classification was somewhat arbitrary, it was done prospectively without any knowledge of SF-36 results and did seem clinically relevant. Dr Butler, who did an advance reading of the manuscript, noted that in the asymptomatic group in the domain of mental health, the comparison of postoperative with preoperative scores showed significant improvement but that the mean for the preoperative score (78) was higher than the national norm (75). (See Table 3 in the article.) Those scores were not statistically different. But the aggregate improvement in 43 patients postoperatively to a mean score of 82 was a highly significant improvement when calculated with a Wilcoxon rank sum statistic. Remember that a score of 100 is perfect mental health.

This short video demonstrated the long interest that Virginia Mason has had in health-related quality of life in hyperparathyroidism. This movie was made in 1951 by Dr Joel Baker, who of course was president of the PCSA over 30 years ago. Here is Dr Baker talking about a middle-aged woman with hyperparathyroidism. Here she is pictured on the roof of Virginia Mason barely able to climb the steps. Note the view of Puget Sound. Here is the parathyroid at the time of the operation. It was so big that it was localized by barium swallow, and Dr Baker only explored one side of the neck. Here is the patient postoperatively back up on the roof. We didn’t have the SF-36, but boy, look how spry this patient is now: up and down the steps, tying her shoes, and giving a huge bow to Dr Baker!

---

**Surgical Anatomy**

There are 2 types of diaphragmatic hernia: Bochdalek (posterolateral), more common on the left than the right; and Morgagni, or anterior parasternal hernia.