Impact of Surgical Treatment on Respiratory Muscle Dysfunction in Symptomatic Hyperparathyroidism

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Hypothesis: We hypothesized that surgical treatment would improve respiratory muscle strength in symptomatic hyperparathyroidism (HPT).

Design: Prospective clinical trial.

Setting: A tertiary referral center.

Patients: Fifteen consecutive patients with symptomatic HPT and 10 with euthyroid multinodular goiter (control group) without a history of obstructive or restrictive lung disease.

Interventions: Forced vital capacity and forced expiratory volume in 1 second were measured before and 6 months after surgery to estimate respiratory muscle involvement. These measurements were compared with the reference values estimated individually in each patient. Mann-Whitney and Wilcoxon signed rank tests were used for statistical analysis, and P<.05 was considered statistically significant.

Main Outcome Measures: Respiratory dysfunction in patients with symptomatic HPT, pulmonary function after parathyroidectomy, and the correlation between the preoperative serum parathyroid hormone and total serum calcium values and the impairment in pulmonary function.

Results: Preoperative forced vital capacity and forced expiratory volume in 1 second measurements were below the reference values in 11 (73%) and 9 (60%) patients, respectively. All the patients were normocalcemic, and forced vital capacity and forced expiratory volume in 1 second measurements significantly improved at postoperative month 6 (P=.001). No significant difference was detected in the control group. Improvement in pulmonary function correlated with preoperative serum calcium and parathyroid hormone values in patients with HPT (P<.05 and P<.001, respectively).

Conclusions: Symptomatic HPT impairs inspiratory and expiratory components of respiratory function, and normalization of serum calcium levels after surgical treatment is associated with a significant improvement in lung function.

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Hyperparathyroidism (HPT) is frequently associated with neuromuscular dysfunction, and symptoms related to muscle weakness constitute the leading manifestations in patients with symptomatic HPT (sHPT).1 Previous studies2-6 investigating muscular performance in HPT concentrated on extremity muscles and documented deterioration of muscle strength improving significantly after successful surgical treatment. Hyperparathyroidism can be symptomatic or asymptomatic (aHPT). Although symptoms and associated conditions related to HPT have previously been defined as sHPT, there is not a clear definition to distinguish between sHPT and aHPT.1 Most patients preoperatively defined as having aHPT experienced subjective improvement after parathyroidectomy, and approximately 5% truly had aHPT.1,9

Postoperative improvement in muscular performance correlated with preoperative serum calcium levels in sHPT.2,6,7 There are limited studies9-13 concerning the effect of HPT and parathyroidectomy on respiratory muscle strength. The HPT state was found to be a preoperative risk factor for decreasing peak expiratory flow.10 Lung function test results improved significantly with normalization of serum calcium levels after surgical treatment, but no correlation was detected between the postoperative improvement and the preoperative values of serum calcium and parathyroid hormone (PTH).11 The aim of this prospective study is to evaluate the status of the respiratory muscle function in sHPT, the impact of successful surgical treatment, and the correlation between the

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FEV1 measurements were used to estimate the impairment in pulmonary function tests before and 6 months after surgical treatment. Forced vital capacity (FVC) and FEV1 were measured using Vmax 229 (SensorMedics, Yorba Linda, Calif) and dry spirometry before and 6 months after the surgical intervention. Reference ranges for FVC and FEV1 were estimated individually in each patient, and values below these ranges constituted impairment in lung function.

This study was conducted in the General Surgery Department of Istanbul Medical Faculty between September 1, 2002, and December 1, 2003. Fifteen consecutive patients with sHPT and 10 with euthyroid multinodular goiter (control group) without a history of restrictive or obstructive pulmonary disease were included. Patients with sHPT were defined as having HPT by biochemical analysis and symptoms or associated conditions related to HPT. Of 15 patients with sHPT, 14 had the primary form and 1 had the tertiary form. Assays of serum intact PTH (iPTH), total calcium, blood urea nitrogen, creatinine, and alkaline phosphatase were performed in all patients before and 6 months after surgical treatment. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) were measured to evaluate respiratory muscle involvement. The FVC and FEV1 measurements were used to estimate the impairment in inspiratory and expiratory functions, respectively. Pulmonary function tests were performed using Vmax 229 (SensorMedics, Yorba Linda, Calif) and dry spirometry before and 6 months after the surgical intervention. Reference ranges for FVC and FEV1 were estimated individually in each patient, and values below these ranges constituted impairment in lung function.

The aims of this study are to investigate whether patients with sHPT have respiratory dysfunction, to evaluate the impact of parathyroidectomy on pulmonary function, and to document the correlation between the preoperative values of serum PTH and total calcium and the impairment in pulmonary function. The results of pulmonary function tests before and 6 months after surgery were compared to evaluate the impact of surgical treatment on sHPT-related respiratory dysfunction. The relationships between the postoperative improvement in pulmonary function test results and preoperative total serum calcium and PTH values were investigated to reveal any correlation. The results are given as mean ± SD. Mann-Whitney and Wilcoxon signed rank tests were used for statistical analysis, and P < .05 was considered statistically significant. The study was approved by the local ethics committee of Istanbul Medical Faculty, and informed consent was obtained from all the patients.

### Method

**Preoperative Findings**

- Of 15 patients with sHPT, 13 (87%) were women and 2 (13%) were men, with a mean age of 49 ± 13.3 years. The control group consisted of 7 women and 3 men, with a mean age of 48 ± 11.4 years. There was no significant difference between the study and control groups in terms of age and sex. None of the controls had a large goiter that might cause tracheal compression. On the preoperative questionnaire, generalized fatigue and muscular weakness were the common complaints of all 15 patients with sHPT, followed by constipation (n = 6; 40%) and depression (n = 6; 40%). None of the patients with HPT had shortness of breath at rest, but they all complained of exhaustion with minimal effort. A history of nephrolithiasis was present in 2 patients (13%), and 2 patients had had bone fractures.

- Ultrasonography and subtraction scintigraphy revealed a single parathyroid adenoma in 14 patients (93%) and bilateral involvement in the 1 patient with tertiary HPT (7%). Preoperative mean values of total serum calcium, total phosphorus, total sodium, serum urea nitrogen, creatinine, and alkaline phosphatase are given in Table 1. Blood urea nitrogen and creatinine levels were within the reference ranges in all 15 patients except the 1 with tertiary HPT (serum phosphorus, 4.5 mg/dL [1.1 mmol/L]). None of the patients with HPT had shortness of breath at rest, but they all complained of exhaustion with minimal effort. A history of nephrolithiasis was present in 2 patients (13%), and 2 patients had had bone fractures.

- All the patients underwent bilateral neck exploration. Parathyroid adenoma excision was performed in 14 patients with solitary adenomas, and subtotal resection was performed in 1 patient with hyperplasia. Near total thyroidectomy (lobectomy and contralateral subtotal resection) was performed in 10 patients with multinodular goiter in the control group.

### Results

#### Preoperative Findings

Of 15 patients with sHPT, 13 (87%) were women and 2 (13%) were men, with a mean age of 49 ± 13.3 years. The control group consisted of 7 women and 3 men, with a mean age of 48 ± 11.4 years. There was no significant difference between the study and control groups in terms of age and sex. None of the controls had a large goiter that might cause tracheal compression. On the preoperative questionnaire, generalized fatigue and muscular weakness were the common complaints of all 15 patients with sHPT, followed by constipation (n = 6; 40%) and depression (n = 6; 40%). None of the patients with HPT had shortness of breath at rest, but they all complained of exhaustion with minimal effort. A history of nephrolithiasis was present in 2 patients (13%), and 2 patients had had bone fractures.

Ultrasonography and subtraction scintigraphy revealed a single parathyroid adenoma in 14 patients (93%) and bilateral involvement in the 1 patient with tertiary HPT (7%). Preoperative mean values of total serum calcium, iPTH, serum urea nitrogen, creatinine, and alkaline phosphatase are given in Table 1. Blood urea nitrogen and creatinine levels were within the reference ranges in all 15 patients except the 1 with tertiary HPT (30 mg/dL [10.7 mmol/L] and 1.5 mg/dL [133 µmol/L], respectively. Preoperative measurements of FVC and FEV1 were below the reference values in 11 patients (73%) and 9 (60%), respectively (Table 2). Pulmonary function test results were within the reference ranges in the control group (Table 3).

### Operative Findings

All the patients underwent bilateral neck exploration. Parathyroid adenoma excision was performed in 14 patients with solitary adenomas, and subtotal resection was performed in 1 patient with hyperplasia. Near total thyroidectomy (lobectomy and contralateral subtotal resection) was performed in 10 patients with multinodular goiter in the control group.

### Postoperative Findings

Biochemical analysis and pulmonary function test results were performed in both groups 6 months after surgical intervention. All the patients were normocalcemic 6 months after surgery. Postoperative mean values of total serum calcium (9.1 ± 0.3 mg/dL [2.28 ± 0.08 mmol/L]) and iPTH (104 ± 66 pg/mL) were found to be significantly lower than...
preoperative values in patients surgically treated for HPT (P<.001) (Table 1). Despite significant decreases, serum iPTH and alkaline phosphatase levels remained elevated in 10 and 4 patients, respectively. Both FVC and FEV₁ improved significantly compared with preoperative values (P<.001) (Table 3 and Figure 1). Improvement in pulmonary function was found to have a linear correlation with preoperative total serum calcium (P=.02 for FVC; P=.04 for FEV₁) and iPTH values (P<.001) (Figure 2 and Figure 3). In 3 patients (patients 1, 9, and 15), no significant difference was observed between the preoperative and postoperative measurements of FVC (2276.6±444.5 mL vs 2780.0±430.0 mL; P=.1) and FEV₁ (2576.6±585.4 mL vs 2613.4±605.8 mL; P=.1) (Figure 1). The postoperative measurements of FVC and FEV₁ were significantly higher than the preoperative values in the remaining 12 patients (2242.5±603.7 mL vs 2611.6±582.3 mL, P=.002; and 1970.8±519.2 mL vs 2415.0±517.0 mL, P=.002, respectively) (Figure 1). The preoperative values of total serum calcium and iPTH were lower and the age was younger in the 3 patients having no significant postoperative improvement in respiratory function compared with the remaining 12 patients with significant postoperative improvement, but the results were not significant (10.8±0.06 mg/dL [2.7±0.02 mmol/L] vs 12.50±1.53 mg/dL [3.13±0.38 mmol/L], P=.1; 148±28 pg/mL vs 513±638 pg/mL, P=.1; and 46.3±4.9 years vs 49.8±17.05 years, P=.6, respectively). The postoperative results of pulmonary function tests were not significantly different than the preoperative values in the control group (Table 3).

**COMMENT**

In this study, the effect of sHPT on respiratory muscles and the impact of parathyroidectomy were investigated by measuring FVC and FEV₁ before and 6 months after surgery. Patients surgically treated for euthyroid multinodular goiter served as the control group. Impairment in pulmonary function, involving expiratory and inspiratory capacity, was found in most patients with sHPT, and surgical treatment resulted in significant improvement. The postoperative improvement in pulmonary function was found to have a linear correlation with preoperative total serum calcium and iPTH values. In 3 patients (patients 1, 9, and 15), no significant difference was observed between the preoperative and postoperative measurements of FVC and FEV₁, but the results were not significant compared with the remaining 12 patients with significant postoperative improvement. The preoperative values of total serum calcium and iPTH were lower and the age was younger in the 3 patients having no significant postoperative improvement in respiratory function compared with the remaining 12 patients with significant postoperative improvement, but the results were not significant.
tion correlated with preoperative levels of total serum calcium and iPTH. Younger patients with relatively low preoperative total serum calcium and iPTH values had no significant difference in preoperative and postoperative lung function. Surgical treatment was successful and all the patients were normocalcemic 6 months after surgery. Although serum iPTH and alkaline phosphatase levels significantly decreased after surgery, they were still high in most patients. We believe that high postoperative levels of serum iPTH might be related to sHPT in this study. Persistent elevation of serum PTH levels in normocalcemic patients after surgical treatment of HPT has previously been reported, although the exact pathogenesis was unclear.14-18 High levels of serum PTH after successful surgery might be associated with advanced disease, extensive bone involvement, and increased bone turnover in the postoperative period.15-17

Muscle strength in HPT has been evaluated using dynamometry, ergometry, electromyography, muscle biopsy, measurement of handgrip strength, subjective measurements, and a fatigue scale.2,3,19,20 Proximal muscle groups of extremities were mainly preferred for dynamometric and ergonomic studies and electromyography. Muscle function was found to be impaired in HPT, and it significantly improved after surgical treatment in most related studies, although some studies documented no significant preoperative impairment or postoperative improvement in muscle function, especially in mild HPT.2,8,10-21 In studies of patients with marked hypercalcemia, muscle function improved significantly after surgical treatment for HPT, and the improvement correlated with preoperative serum calcium levels.2,6,7

Although serum calcium has an important role in muscle contraction, the exact mechanism of impairment in muscle function in HPT is still obscure. Impairment in nerve conduction velocity, neuromuscular transmission, glycolytic enzyme activity, and structural changes in muscle fibers were suggested as possible mechanisms.12,22,23 Significant improvement in isometric and isokinetic muscle strength after parathyroidectomy suggested that type II muscle fibers were pre-

dominantly affected in HPT.2,3,7,10 Advanced HPT was associated with atrophy of type II muscle fibers, and levels of glycolytic enzymes, which dominate in type II fibers, significantly increased after surgical treatment of HPT.19 Excess PTH resulted in amino acid release from skeletal muscle cells in an experimental study.24 These data support the findings of Joborn et al2 and Ljunghall et al,22 who documented nerve function and neuromuscular transmission to be normal in patients with HPT and suggested that the reason for muscle weakness resided in the muscle itself.

Muscle weakness associated with HPT was well documented in extremity muscles, but studies concerning the effect on respiratory muscles were limited. In a study investigating preoperative risk factors in 123 patients with HPT, peak expiratory flow was found to be significantly decreased compared with that of the control group.10 Kristofofferson et al11 reported the results of a prospective study evaluating the status of respiratory muscles in HPT and the impact of surgical treatment. Maximal expiratory and inspiratory breathing pressures were measured before and 6 to 12 months after surgery in patients with HPT. Preoperative lung function test results were within the reference ranges in all but 1 patient. Normalization of hypercalcemia improved respiratory muscle function, as verified by the significant increase in maximal expiratory pressure only and not in maximal inspiratory pressure.11 No significant correlation was reported between the improvement in respiratory function and preoperative values of serum calcium and PTH.11 In the present study, we used FEV₁ and FVC measurements to elucidate the status of respiratory muscles. Contrary to findings from Kristofofferson et al,11 we found significant impairment in pulmonary function in most patients with sHPT. Both FEV₁ and FVC significantly improved after surgery, suggesting that inspiratory and expiratory lung function improved, and the improvement correlated with preoperative values of serum calcium and PTH. A possible reason for this discrepancy between the 2 studies might be the differences in patient characteristics. Median total serum calcium and PTH values were lower in patients in the study by Kristofofferson et al11 than
in our patients. Symptomatic HPT associated with marked hypercalcemia was present in all of our patients and was complicated by pathological fractures in 2 (13%). Inspiratory capacity mainly depends on diaphragmatic function; therefore, it may be postulated that prolonged marked hypercalcemia causes dysfunction in diaphragmatic muscles and in other respiratory muscles.

Most patients with HPT are diagnosed at an advanced stage in Turkey, and all the patients in this study had sHPT, although they were consecutively treated. Therefore, the data collected from the present study refer to the impairment of respiratory function only in patients with sHPT. Further studies are needed to reveal any respiratory function involvement in patients with aHPT.

In conclusion, inspiratory and expiratory components of pulmonary function are deteriorated in sHPT. Impairment of pulmonary function is reversible and significantly improves after successful surgical treatment. Improvement in respiratory function correlates with preoperative values of serum calcium and PTH. In the preoperative management of patients with sHPT, note that inspiratory and expiratory capacity might be seriously impaired, especially in patients with severe hypercalcemia.

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