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RESEARCH

Impact of parathyroidectomy on quality of life in multiple endocrine neoplasia type 1

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Abstract

Background: Potential influences of parathyroidectomy (PTx) on the quality of life (QoL) in multiple endocrine neoplasia type 1-related primary hyperparathyroidism (HPT/MEN1) are unknown.
Method: Short Form 36 Health Survey Questionnaire was prospectively applied to 30 HPT/MEN1 patients submitted to PTx (20, subtotal; 10, total with autograft) before, 6 and 12 months after surgery. Parameters that were analyzed included QoL, age, HPT-related symptoms, general pain, comorbidities, biochemical/hormonal response, PTx type and parathyroid volume.
Results: Asymptomatic patients were younger (30 vs 38 years; $P = 0.04$) and presented higher QoL scores than symptomatic ones: Physical Component Summary score (PCS) 92.5 vs 61.2, $P = 0.0051$; Mental Component Summary score (MCS) 82.0 vs 56.0, $P = 0.04$. In both groups, QoL remained stable 1 year after PTx, independently of the number of comorbidities. Preoperative general pain was negatively correlated with PCS ($r = -0.60$, $P = 0.0004$) and MCS ($r = -0.57$, $P = 0.0009$). Also, moderate/intense pain was progressively (6/12 months) more frequent in cases developing hypoparathyroidism. The PTx type and hypoparathyroidism did not affect the QoL at 12 months although remnant parathyroid tissue volume did have a positive correlation ($P = 0.0490$; $r = 0.3625$) to PCS 12 months after surgery. Patients with one to two comorbidities had as pre-PTx PCS ($P = 0.0015$) as 12 months and post-PTx PCS ($P = 0.0031$) and MCS ($P = 0.0365$) better than patients with three to four comorbidities.
Conclusion: A variable QoL profile was underscored in HPT/MEN1 reflecting multiple factors associated with this complex disorder as comorbidities, advanced age at PTx and presence of preoperative symptoms or of general pain perception. Our data encourage the early indication of PTx in HPT/MEN1 by providing known metabolic benefits to target organs and avoiding potential negative impact on QoL.

Key Words
- quality of life
- multiple endocrine neoplasia type 1
- parathyroidectomy
- hyperparathyroidism
- hypoparathyroidism

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Background

Multiple endocrine neoplasia type 1 (MEN1) (#131100) is an autosomal dominant inherited syndrome mainly caused by germline mutations in the *MEN1* tumoral suppressor gene (1, 2). Most mutation carriers will develop at least one of the main endocrine tumors at the age of 50 years with the following estimated prevalence: primary hyperparathyroidism (pHPT) (82–100%), enteropancreatic (30–80%) and pituitary tumors (15–65%) (1, 2, 3, 4, 5). Due to its higher penetrance and earlier onset, pHPT accounts for the first biochemical and/or clinical manifestation in up to 75% of the MEN1 patients (1, 6, 7, 8, 9).

The molecular diagnosis of *MEN1* carriers has allowed the earlier diagnosis of MEN1-related tumors by periodic hormonal and radiologic screening (1, 6, 8, 9, 10, 11). Therefore, young patients are predominantly asymptomatic at the time of pHPT diagnosis (1, 2, 6, 9, 11). Although parathyroidectomy (PTx) is the consensual treatment for MEN1-related pHPT (HPT/MEN1), the ideal timing to perform the operation in asymptomatic patients, especially in young individuals, remains under debate (2, 11, 12, 13).

Patients with HPT/MEN1 frequently require bilateral neck exploration as parathyroid disease is mostly multiglandular. Accordingly, the two elective surgical techniques recommended for HPT/MEN1 are total PTx with heterotopic autograft (TPTx+AG) and subtotal PTx (SPTx) (2, 13, 14).

Although permanent hypoparathyroidism (HYPO) after PTx is an uncommon event in sporadic pHPT (15, 16), it is a matter of concern in HPT/MEN1 patients, as HYPO occurs in up to 50 and 35% of the patients undergoing TPTx+AG and SPTx, respectively (14). The high frequency of permanent HYPO in HPT/MEN1 patients may be due to multiple factors such as multiple neck explorations by asynchronous parathyroid involvement, simultaneous total thyroidectomy and low autograft secretory function as a result of surgical, technical/anatomical difficulties or limited healthy parathyroid tissue available.

As HYPO is expected to be associated with lower quality of life (QoL), either by its symptoms or by the treatment of hypocalcemia (17), the extent of the surgical procedure and its ideal timing in oligo- or asymptomatic HPT/MEN1 patients should be carefully considered (11, 12). Also, less-extensive surgeries in HPT/MEN1 have their downsides and may increase the risk of persistence/recurrence of hypercalcemia requiring multiple operations and their possible complications which also impact QoL (18).

In patients with sporadic pHPT, QoL is improved after operation mainly due to a reduction of physical symptoms (19, 20, 21, 22). Even for asymptomatic sporadic patients, a significant gain in QoL after parathyroid surgery has been noted when compared with those in vigilance (23). Also, for renal HPT patients, another condition of multiglandular parathyroid disease, an improvement of QoL occurs after SPTx and TPTx+AG, but these patients are often highly symptomatic before surgery (24, 25). In turn, prospective studies focusing on the role of PTx on QoL in MEN1 are absent.

In the last two decades, an increasing interest in QoL of MEN1 patients has been observed. Most papers were accounted for cross-sectional studies focusing on different aspects of QoL applying questionaries sent by mail or web-based to MEN1 patients (26, 27, 28, 29, 30). Only one study analyzed the QoL at two different times (at the hospitalization for various reasons and 6 months after) (31). Overall, these papers have revealed lower QoL indexes compared to the general population, with sporadic HPT or with other chronic conditions (18, 27, 28, 30, 31). Also, different factors were associated with worse QoL in MEN1 patients such as financial burden, persistent hyperparathyroidism, increased travel distance and higher frequency of doctor appointments/year, younger age at diagnosis, employment status and presence of a pituitary tumor or pancreatic neuroendocrine tumor (NET) and high fear of disease occurrence (18, 27, 29, 30). However, other studies have revealed normal global QoL in MEN1 patients (32) with no impact of pancreatic NET on QoL in these patients (18). It was suggested that factors such as better comprehension of disease by access to a specialized clinical Referral Center and continued support of patient associations promote better acceptance and higher adaptative capacity probably contributing to the relative preservation of the QoL for MEN1 patients (26, 32). In a recent review, including the opinion of multidisciplinary team of experts in MEN1 syndrome and the patient advocacy group, healthy-related QoL was selected as one of the future challenges to be better explored and understood, aiming to optimize medical care for MEN1 patients improving the shared decision-making for management and treatment of this disorder (33).

More recently, it has been reported that the phenotype and outcome of MEN1 phenocopies (mutation-negative MEN1 cases) are different in patients harboring a *MEN1* mutation with a potential future impact on the surgical and clinical management (34). Importantly, the genetic diagnosis of cases included in some previous studies approaching QoL in MEN1 are neglected or phenocopies were not excluded (18, 26, 27, 28, 32).

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From our knowledge, there is no longitudinal study addressing the influence of PTx in HPT/MEN1 patients on QoL. Thus, this prospective study intends to, as a primary outcome, investigate the QoL parameters before and up to 1 year after PTx in HPT/MEN1 patients carrying a germline *MEN1* mutation. Further, as a secondary outcome, the role of multiple peri-PTx factors that carry a potential risk of interfering with QoL will be explored.

Method

This prospective study, performed from November, 2015, to February, 2019, addressed primarily the influence and the impact of PTx on QoL in patients with HPT/MEN1. As secondary outcome, the role of the following multiple perioperative factors on QoL were approached: HPT-related symptoms, MEN1-associated comorbidities, PTx type, parathyroid volume and development of HYPO.

Patients and ethical aspects

The present study was approved by the Institutional Ethics Review Board (CEP; register number – CAAE: 49697715.6.0000.0068), and all patients signed an informed consent form.

At admission, all patients with the clinical diagnosis of MEN1 have been routinely offered genetic testing in our Institution since 2004 (35). All patients meeting the criteria for PTx for HPT/MEN1 (described below) were invited by one surgeon (MDGB) to participate in the present prospective study in our single tertiary center. Only patients carrying germline *MEN1* mutations were included in the final analysis.

HPT was defined as hypercalcemia associated with high levels of PTH or normal/high calcium values and high or inappropriately normal values of PTH.

Persistent disease was considered when serum calcium was elevated until 6 months after PTx. Recurrence was defined when calcium levels and PTH were increased 6 months after PTx.

HYPO was considered when there was a need to maintain therapy with calcium (≥1.0 g/day) or in association with calcitriol to secure normal calcium, irrespective of calcium supplements routinely offered to achieve recommended daily intake.

Active investigation of the following comorbidities was provided to all patients: functioning and non-functioning pituitary tumor, functioning and non-functioning pancreatoduodenal NET, other MEN1-related NETs (thymic and bronchial), malignant tumors (breast, colon and thyroid) and diabetes (type 2 and/or post-pancreatectomy).

Inclusion criteria

The inclusion criteria involved patients who fulfilled the criteria for clinical diagnosis of MEN1 and carried a germline *MEN1* mutation, returned to the 6- and 12-month follow-up and replied the two applied questionnaires.

Exclusion criteria

Exclusion factors involved patients with not confirmed germline *MEN1* mutation, those who failed to answer the QoL questionnaire at any scheduled moment, cases submitted to less than SPTx, and cases with previous anterior cervical exploration, including PTx or thyroidectomy. We considered less than SPTx when up to three parathyroid glands were identified and/or resected.

Genetic diagnosis

Extraction of genomic DNA, Sanger sequencing covering coding/splicing regions of the *MEN1* gene and Multiplex Ligation-dependent Probe Amplification Assay (MLPA) for investigation of large deletions were conducted as previously reported (10, 35, 36).

Indications for operation

Surgical treatment was recommended to all symptomatic HPT/MEN1 patients. Except for age (<50 years), all asymptomatic individuals were advised to surgery if they met any of the following criteria established by the Consensus for Asymptomatic Sporadic pHPT (37): (i) patients with total calcium 1.0 mg/dL above the upper limit of the normality; (ii) low bone mass for age and/or vertebral fractures; (iii) nephrolithiasis or nephrocalcinosis detected by imaging studies; (iv) creatinine clearance <60 mL/min; (v). Twenty-four-hour urinary calcium excretion ≥400 mg/dL or ≥4mg/kg. Also, the presence of gastrinoma was considered as an additional criterion for surgery (1, 38, 39).

Type of PTx in HPT/MEN1 patients

The operative strategy for each patient was at the surgeon's discretion mainly based on intraoperative findings: macroscopic aspect of parathyroid glands, local anatomy, the need for concomitant thyroidectomy, viability

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of parathyroid tissue after dissection and associated morbidities that may increase surgical and anesthetic risks in future procedures. Also, all patients were routinely submitted to prophylactic thymectomy (40).

SPTx was performed by complete resection of three parathyroid glands and part of the fourth, leaving a stump of approximately the size of two normal glands (2, 41). TPTx+AG corresponded to the resection of all identified parathyroids and the immediate forearm autograft of 30–45 parathyroid fragments measuring 2 × 1 × 1 mm.

All identified parathyroid tissue was measured in its three dimensions with a millimetric scale ruler after excision or indirectly using the distance between the points of a Mixter clamp transposed to a millimetric scale as a surrogate measure in the case of the remaining tissue in the SPTx. The total volume of each PT was calculated with the ellipsoid formula, $V = 4/3 \times \pi \times a \times b \times c$, where a, b and c accounted for the three observed measures of the parathyroid glands. Remnant parathyroid tissue volume of the stump in SPTx was also measured in its three dimensions while the total volume of the autografted tissue in TPTx+AG was estimated by sum of the volume from fragments used.

QoL questionnaire

During the preoperative hospitalization and every 6 months after surgery, a psychologist (KCR, blinded about surgical method planned) applied the Short Form 36 Health Survey Questionnaire (SF-36) (42). The questionnaire contains 36 questions that investigate eight different domains of QoL: physical functioning (PF), role-functioning physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-functioning emotional (RE) and mental Health (MH). The eight domains were computed and transformed to a 0–100 scale, with lower scores representing worst QoL in terms of the dimensions studied. Two components summarized the following measures: Physical Component Summary (PCS) – calculated as the mean of PF, RP, BP and GH scores – and Mental Component Summary (MCS) – calculated as the mean of the VT, SF, RE and MH scores (43). SF-36 scores were calculated from the available formula: http://www.rand.org/health/surveys_tools/mos/36-item-short-form/scoring.html.

Changes of both PCS and MCS (43) were estimated according to preoperative symptoms, including pain, type of surgery (TPTx+AG and SPTx) and postoperative HYPO.

The absolute changes of PCS (Δ PCS) and of MCS (Δ MCS) were calculated by subtracting preoperative from postoperative measurements. The degree of change was considered of clinical significance when Δ MCS or Δ PCS was larger than five points (22, 44, 45). Accordingly, patients were stratified in groups as WORSE (Δ ≤−5), STABLE (−5< Δ <+5) or BETTER (Δ ≥+5) in PCS and MCS.

Symptoms

Preoperative symptoms evaluated were bone pain, fatigue and/or weakness and pain episodes related to renal stones.

The patients were required to answer about pain considering two aspects: (i) categorical answer (yes or no) made by physicians (MDGB and DMLJr) and then analyzed as symptomatic or not for bone pain; (ii) Numeric Rating Scale (NRS) for referred general pain (46) was applied by the psychologist (KCR) immediately before the answer to the SF-36 questionnaire. The analysis included the stratification of pain as mild (1–4), moderate (5–6) and severe (7–10) (47).

Biochemical measures

The biochemical parameters evaluated were serum levels of total calcium (reference range, 8.6–10.2 mg/dL), phosphorus (2.7–4.5 mg/dL), total alkaline phosphatase (AP) (35–130 UI/L) and $25(OH)_2$ vitamin D (VitD) (deficiency <10 ng/mL; insufficient 10–30 ng/mL; appropriate 30–100 ng/mL; toxicity >100 ng/mL). Intact parathyroid hormone levels (PTH) (10–65 pg/mL) were measured using a chemiluminescence assay (DPC, Medlab, San Antonio, TX, USA). All biochemical measures were performed at the time of the preoperative hospitalization, 6 and 12 months after surgery.

Composition of casuistic

Overall, 57 patients with clinical and/or genetic diagnosis of HPT/MEN1 underwent PTx. Sixteen were ineligible and 11, whose clinical characteristics are depicted at Table 1, were excluded by different reasons (Fig. 1).

Statistical analysis

Continuous variables were tested for normality with Kolmogorov–Smirnov test. If the distribution passed the test for normality, they are presented as mean ± S.D. in some tables. On the other hand, non-parametric distributions were summarized as median and first (Q1) and third quartile (Q3). In order to make comparison easier, we presented normal data as median and Q1–Q3 in tables if

Table 1 Mean values (pre- and post-parathyroidectomy) of biochemical/hormonal data and of QoL scores in 30 HPT/MEN1 patients studied and basal values of 11 patients excluded. Data presented as median and interquartile range (Q1-Q3).

Parameter	Included patients (n = 30)				Excluded patients (n = 11)
	Preoperative	6 months	12 months	P value	Basal
Age (years)	38 (28–44)	–	–	–	33 (24–43)
Ca (mg/dL)	**10.8 (10.4–11.1)**	**9.4 (8.9–10.1)**	**9.4 (9.0–9.9)**	**<0.0001**[c]	10.7 (10.0–11.1)
P (mg/dL)	**2.6 (2.3–3.2)**	**3.4 (3.0–3.8)**	**3.2 (2.8–3.6)**	**<0.0001**[c]	2.6 (2.0–3.4)
PTH (pg/mL)	**104 (76–137)**	**32 (17–50)**	**35 (24–46)**	**<0.0001**[c]	133 (65–198)
AP (IU/L)	**86 (74–114)**	**67 (52–84)**	**69 (56–84)**	**<0.0001**[c]	62 (51–120)
VitD (ng/mL)	**21.2 (17.0–23.4)**	**30.7 (25.2–37.4)**	**28.8 (23.0–40.7)**	**<0.0001**[c]	21 (17.4–25)
PCS	76 (44–91)	72 (51–92)	80 (46–92)	0.71	81.5 (50.25–91.75)
MCS	66 (36–84)	75 (33–87)	76 (45–89)	0.23	74.8 (45–85.8)
PF	88 (59–100)	90 (64–100)	85 (64–96)	0.57[a]	95 (60–100)
RP	100 (0–100)	84 (0–100)	100 (0–100)	0.22[a]	100 (0–100)
BP	88 (41–100)	61 (41–100)	72 (28–100)	0.23[a]	74 (71–100)
GH	62 (40–77)	62 (44–82)	60 (39–77)	0.55[b]	67 (42–87)
VT	60 (30–81)	62 (40–80)	65 (39–75)	0.51[b]	70 (45–85)
SF	**69 (38–100)**	**88 (57–100)**	**82 (50–100)**	**0.04**[a,c]	63 (38–100)
RE	100 (0–100)	84 (0–100)	100 (0–100)	0.22[a]	100 (33–100)
MH	66 (43–80)	70 (44–88)	72 (44–84)	0.23[b]	68 (52–76)

[a]Calculated by Friedman test, [b]Calculated by ANOVA; [c]Six and 12 months compared to preoperative.
Bold indicates statistical significance, $P < 0.05$.
AP, alkaline phosphatase; BP, bodily pain; GH, general health perceptions; HPT/MEN1, multiple endocrine neoplasia type 1-related primary hyperparathyroidism; MH, mental health; MCS, Mental Component Summary score; PF, physical functioning; PCS, Physical Component Summary score; PTH, parathormone; QoL, quality of life; RE, role-functioning emotional; RP, role-functioning physical; SF, social functioning; VT, vitality; VitD, $25(OH)_2$ vitamin D.

at least one variable had a non-parametric distribution, as in normal distributions, the mean and the median are usually similar. Considering inferential statistics, we used unpaired or paired Student's *t*-test, Kruskal–Wallis (with Dunn's multiple comparison test), ANOVA or Bonferroni's multiple comparison method, Friedman and Mann–Whitney tests. Correlations were analyzed with the Spearman's r test. All data compiled for statistical analysis were processed in GraphPad Prism1 version 7.0a software. Patients were stratified according to the presence/absence of symptoms, pain intensity, comorbidities, type of PTx, the condition of HYPO and changes in PCS or MCS in contingency tables and compared using the Fisher's exact test, Wilcoxon test or the chi-square test.

In addition, analysis of the effect' size (r) was selected to validate correlations on QoL. Cohen's test was applied to parametric samples while the following formula was applied to non-parametric ones: (r = |Z|/sqrt(N)), where

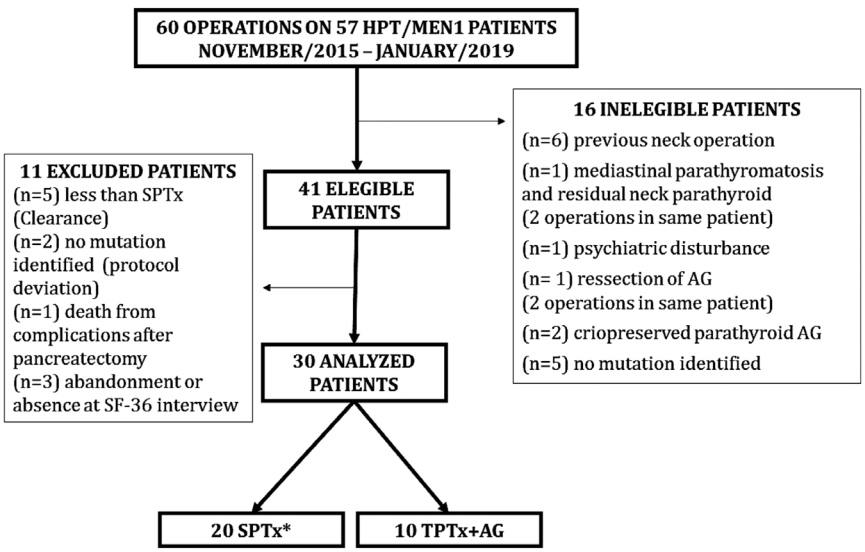

Figure 1
Flow diagram of included patients. *(n = 1) neck re-operation by persistence of HPT. AG, autograft; HPT/MEN1, multiple endocrine neoplasia type 1-related primary hyperparathyroidism; SPTx, subtotal parathyroidectomy; SF-36, Short Form 36 Health Survey Questionnaire; TPTx+AG, total parathyroidectomy with autograft.

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the absolute value Z is divided by the square root of the sample size. The interpretation of values for r is: 0.10 to <0.3 (small effect), 0.30 to <0.5 (moderate effect) and ≥0.5 (large effect).

Results

Overall features

The biochemical/hormonal data and SF-36 summary scores of the 30 (TPTx+AG, 10; SPTx, 20) HPT/MEN1 patients (16 female) before and after PTx are shown in Table 1. The median age at the time of PTx was 38 years (Q1-Q3: 28–44 years).

Preoperatively, there was no significant correlation between age, biochemical/hormonal parameters as Ca, P, AP, VitD, PTH or SF-36 summary scores (PCS and MCS).

As expected, there were significant postoperative changes in biochemical/hormonal values (Table 1). At 12 months after surgery, 23 patients (76.7%; 23/30) had normal calcium metabolism and one of seven with HYPO was reoperated by persistent HPT (TPTx+AG) 8 months after the initial procedure (SPTx). This patient was included in the SPTx group as an intention to treat. None had recurrent HPT.

Concerning QoL parameters, no significant difference occurred in PCS or MCS scores postoperatively (Table 1). Overall, median QoL scores remained stable 1 year after PTx as a result of high individual variability of the PCS and MCS values (Table 1 and Supplementary Figs 1, 2, see section on supplementary materials given at the end of this article). The only domain that presented a marginal significant difference was SF (P=0.04) (Table 1).

Symptoms and pain before parathyroidectomy

Preoperatively, 19 HPT/MEN1 patients (19/30; 63.3%) complained of bone pain, 15 had low bone mineral density and 21 cases (21/30; 70%) had nephrolithiasis (clinical-radiological: 14/21; only radiological: 7/21).

No preoperative biochemical/hormonal differences were observed between asymptomatic (11/30; 36.7%) or symptomatic (19/30; 63.3%) patients (Table 2). Asymptomatic patients were significantly younger (P=0.04) and presented diverse parameters of QoL better than observed in symptomatic ones (Table 2). However, Fig. 2 shows the great variability of PCS and MCS observed in an individual basis in these groups, both pre- and postoperatively.

Table 2 Presence or absence of preoperative symptoms. Data are presented as median and interquartile range (Q1-Q3).

Parameter	Symptomatic (n = 19)	Asymptomatic (n = 11)	*P* value
Age (years)	**38 (32–48)**	**30 (22–38)**	**0.04**[a]
SPTx (n = 20)	13 (65%)	7 (35%)	1.00
TPTx +AG (n = 10)	6 (60%)	4 (40%)	–
Ca (mg/dL)	10.7 (10.3–11.1)	10.9 (10.4–11.2)	0.44
P (mg/dL)	2.6 (2.3–3.1)	2.7 (2.4–3.3)	0.35
PTH (pg/mL)	111 (78–171)	101 (58–116)	0.13
AP (IU/L)	88 (75–114)	84 (67–128)	0.82
VitD (ng/dL)	20.3 (16.8–28.0)	23.6 (19.5–25.8)	0.34
PCS	**61.2 (39.5–83.0)**	**92.5 (83.5–94.2)**	**0.0051**[a]
MCS	**56.0 (28.5–75.5)**	**82.0 (46.2–92.2)**	**0.04**[a]
PF	**80.0 (40.0–90.0)**	**100.0 (90.0–100.0)**	**0.0093**[a]
RP	50.0 (0.0–100.0)	100.0 (100.0–100.0)	0.08
BP	62.0 (30.0–100.0)	94.0 (62.0–100.0)	0.14
GH	**47.0 (37.0–67.0)**	**77.0 (62.0–82.0)**	**0.0062**[a]
VT	**45.0 (25.0–70.0)**	**80.0 (55.0–90.0)**	**0.01**[a]
SF	50.0 (25.0–100.0)	88.0 (38.0–100.0)	0.21
RE	100.0 (0.0–100.0)	100.0 (33.0–100.0)	0.30
MH	**56.0 (28.0–72.0)**	**76.0 (64.0–84.0)**	**0.02**[a]

[a]Significantly different by Mann–Whitney test.
Bold indicates statistical significance, $P < 0.05$.
AP, alkaline phosphatase; BP, bodily pain; GH, general health perceptions; MH, mental health; MCS, Mental Component Summary score; PF, physical functioning; PCS, Physical Component Summary score; PTH, parathormone; RE, role-functioning emotional; RP, role-functioning physical; SF: social functioning; SPTx, subtotal parathyroidectomy; TPTx+AG, total parathyroidectomy with autograft; VT, vitality; VitD, $25(OH)_2$ vitamin D.

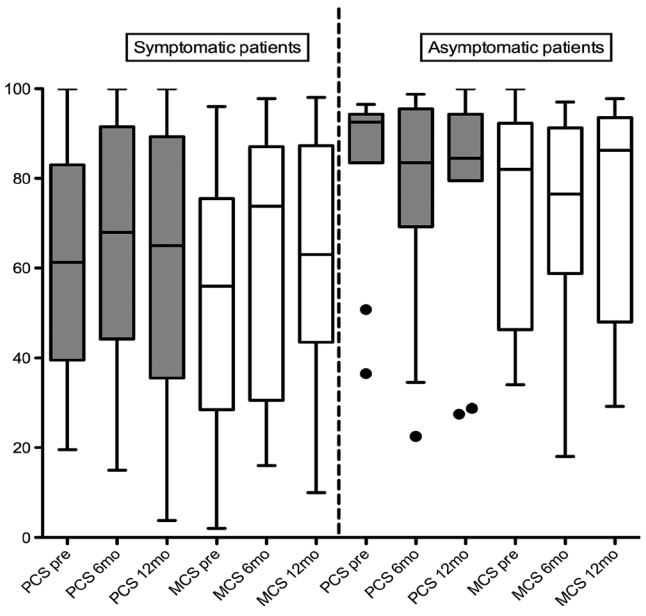

Figure 2
PCS and MCS before and after the operation according to preoperative symptoms. mo, months; PCS, Physical Component Summary score, pre, preoperative; MCS, Mental Component Summary score.

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Table 3 Results of subtotal (SPTx) or total parathyroidectomy with autograft (TPTx+AG) in HPT/MEN1 patients.

Parameter	SPTx (n = 20)			TPTx +AG (n = 10)		
	Preoperative	6 months	12 months	Preoperative	6 months	12 months
Age (years)	38 (30–48)	_	_	38 (25–39)	_	_
Ca (mg/dL)	10.4 (9.5–10.8)	9.4 (8.9–10.1)	9.4 (9.1–9.8)	11.1 (10.2–11.2)	9.4 (8.2–9.9)	9.4 (8.9–10.0)
P (mg/dL)	2.5 (2.2–3.1)	**3.1 (2.8–3.7)**[a]	3.2 (2.7–3.6)	2.9 (2.6–3.3)	**3.8 (3.4–4.3)**[a]	3.4 (2.9–3.9)
PTH (pg/mL)	102 (62–115)	**40 (27–55)**[a]	34 (22–52)	125 (89–217)	**20 (12–31)**[a]	35 (24–41)
AP (IU/L)	78 (68–104)	64 (53–83)	68 (52–84)	102 (82–129)	70 (51–90)	73 (58–86)
VitD (ng/mL)	21.3 (16.8–27.4)	32.2 (27.4–40.2)	30.6 (23.5–42.2)	20.4 (18.5–25.0)	25.4 (23.0–30.4)	26.2 (20.5–33.1)
PCS	93 (83–100)	91 (71–100)	92 (78–100)	90 (63–94)	92 (74–99)	93 (82–100)
MCS	66 (38–83)	70 (34–87)	66 (46–92)	66 (33–88)	82 (32–88)	88 (40–98)
PF	90 (67.5–98.8)	90 (67.5–100)	80 (61.3–98.8)	72.5 (37.5–100)	87.5 (55–96.3)	90 (65–96.3)
RP	100 (46.3–100)	100 (31.3–100)	100 (6.3–100)	25 (0–100)	110 (18.8–100)	100 (75–100)
BP	94 (41–100)	61 (41–98.5)	71 (20–100)	61 (30–100)	67 (48.5–100)	74 (37.5–100)
GH	62 (40.5–79.3)	67 (45.5–82)	59.5 (41.8–75.8)	62 (39.3–75.5)	59.5 (39–84.5)	62 (32.5–80.8)
VT	60 (31.3–78.8)	60 (40–80)	52.5 (40–78.8)	55 (30–86.3)	70 (42.5–81.3)	65 (33.75–71.3)
SF	69 (38–100)	88 (44.3–100)	81.5 (41–100)	62.5 (38–100)	81.5 (53.5–100)	81.5 (50–100)
RE	100 (8–100)	33 (0–100)	100 (0–100)	100 (0–100)	100 (0–100)	100 (24.75–100)
MH	62 (34–79)	66 (44–87)	74 (44–87)	70 (56–80)	82 (45–88)	68 (53–81)

[a]Significantly different from SPTx and TPTx+AG (for PTH $P = 0.04$ and for P $P = 0.004$).
Bold indicates statistical significance, $P < 0.05$.
AP, alkaline phosphatase; BP, bodily pain; GH, general health perceptions; HPT/MEN1, multiple endocrine neoplasia type 1-related primary hyperparathyroidism; MH, mental health; MCS, Mental Component Summary score; PF, physical functioning; PCS, Physical Component Summary score; PTH, parathormone; RE, role-functioning emotional; RP, role-functioning physical; SF, social functioning; SPTx, subtotal parathyroidectomy; VT, vitality; VitD, $25(OH)_2$ vitamin D.

The outcomes of postoperative changes of PCS and MCS scores at 6 and at 12 months stratified by asymptomatic and symptomatic cases with HPT/MEN1 is shown in Supplementary Table 1.

Considering NRS applied before PTx, 21 patients had pain (mild, 8; moderate, 6; severe, 7). There was no correlation between pain score and age or preoperative biochemical/hormonal values, except for AP (r = –0.44, CI –0.69 to –0.08, P=0.0162). Pain score had a significant negative correlation to PCS (r = –0.60, CI –0.80 to –0.30, P=0.0004) and to MCS (r = –0.57, CI –0.78 to –0.26, P=0.0009).

Outcomes of SPTx vs TPTx+AG at 6 and 12 months after parathyroidectomy

Pre- and postoperative results according to the type of PTx are presented in Table 3. The preoperative biochemical/hormonal parameters and QoL scores were similar between patients submitted to SPTx and TPTx+AG and remained similar during postoperative outcome except to significantly lower levels of PTH and higher ones of P at 6 months after TPTx+AG.

QoL and postoperative HYPO vs No HYPO at 12 months after parathyroidectomy

Seven patients (23%) developed HYPO, which was equally frequent in cases submitted to SPTx (5/20, 25%) or TPTx+AG (2/10, 20%). Patients who developed HYPO after PTx were older (P=0.02) (Table 4).

Also, pre- and postoperative QoL scores and biochemical/hormonal parameters were similar between cases with or without HYPO, except to lower values of PCS at 6 months after surgery in cases with HYPO (P=0.0156). However, this difference did not remain significant at 12 months post-PTx, although the median was lower (PCS, P=0.08; MCS, P=1.00) (Table 4).

No significant differences between cases with or without HYPO concerning WORSE, STABLE or BETTER PCS or MCS were observed (PCS, P=0.15; MCS, P=0.61). The absence of statistical significance remained even if cases with BETTER and STABLE PCS or MCS were aggregated and compared to cases with WORSE PCS or MCS (PCS, P=0.0837; MCS, P=1.0). The same results were found when comparing patients with BETTER PCS or MCS against grouped WORSE/STABLE (PCS, P=0.3632; MCS, P=0.4268). Figure 3 shows the wide distribution of PCS and MCS in all moments observed in these patients that may preclude the observation of differences that might exist in individual cases.

The frequency of HYPO was similar in preoperative symptomatic (4/19; 21%) and asymptomatic patients (3/11; 27%; P=1.0).

Preoperative moderate/severe pain complaints occurred more frequently in cases who developed HYPO (4/7, 57%) and increased gradually at 6 (5/7, 71%) and at 12 months (86%, 6/7) (Supplementary Table 2).

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Table 4 Pre- and postoperative aspects of patients with or without HYPO.

Parameter	**NO HYPO** (n = 23[c])			**HYPO** (n = 7[c])		
	Preoperative	6 months	12 months	Preoperative	6 months	12 months
Age (years)	–	–	**34 ± 12**[b]	–	–	**49 ± 16**[b]
SPTx (n = 20)	–	–	15 (75%)	–	–	5 (25%)
TPTx+AG (n = 10)	–	–	8 (80%)	–	–	2 (20%)
Ca (mg/dL)	10.8 (10.3–11.2)	9.4 (8.9–10.1)	9.4 (9.1–9.9)	10.8 (10.5–11.1)	9.1 (6.9–9.9)	9.3 (8.5–9.9)
P (mg/dL)	2.7 (2.3–3.2)	3.4 (3.0–3.8)	3.3 (2.9–3.6)	2.6 (2.4–2.7)	3.2 (3.0–4.3)	2.8 (2.7–3.9)
PTH (pg/mL)	102 (75–129)	37 (26–54)	38 (27–53)	111 (97–233)	18 (8–27)	19 (0–32)
AP (IU/L)	91 (77–114)	72 (60–91)	74 (59–87)	67 (52–75)	52 (36–58)	54 (46–59)
VitD (ng/mL)	21.0 (17.0–28.0)	29.6 (24.8–36.5)	28.7 (22.8–40.3)	21.6 (19.0–25.8)	31.3 (30.2–44.8)	30.4 (23.0–50.4)
PCS	83 (42–90)	80 (63–94)	80 (62–92)	**61 (45–94)**[a]	**56 (32–69)**[a]	36 (28–92)
MCS	66 (42–83)	80 (47–88)	78 (48–90)	46 (28–92)	45 (23–84)	54 (29–89)
PF	90 (65–100)	90 (75–100)	90 (65–100)	75 (40–90)	65 (55–95)	75 (55–90)
RP	100 (25–100)	100 (75–100)	100 (100–100)	100 (0–100)	25 (0–100)	25 (0–100)
BP	94 (41–100)	71 (41–100)	74 (51–100)	62 (40–94)	51 (41–74)	20 (10–94)
GH	62 (40–75)	72 (42–82)	62 (42–77)	77 (37–90)	52 (47–82)	47 (20–87)
VT	65 (30–80)	65 (45–80)	65 (40–75)	50 (30–90)	40 (30–75)	50 (35–75)
SF	75 (38–100)	88 (63–100)	75 (50–100)	38 (38–100)	75 (13–100)	88 (25–100)
RE	100 (32–100)	100 (0–100)	100 (33–100)	33 (0–100)	0 (0–67)	100 (0–100)
MH	68 (40–76)	72 (44–88)	72 (56–84)	64 (44–80)	64 (44–92)	52 (36–88)

[a]Significantly different Wilcoxon matched-pairs signed rank test, $P = 0.0156$; [b]Significantly different by unpaired t-test, $P = 0.02$; [c]Number of cases with HYPO at 12 months after PTx.
Bold indicates statistical significance, $P < 0.05$.
AP, alkaline phosphatase; BP, bodily pain; GH, general health perceptions; HYPO, hypoparathyroidism; MH, mental health; MCS, Mental Component Summary score; PF, physical functioning; PCS, Physical Component Summary score; PTH, parathormone; RE, role-functioning emotional; RP, role-functioning physical; SF, social functioning; SPTx, subtotal parathyroidectomy; TPTx+AG, total parathyroidectomy with autograft; VT, vitality; VitD, $25(OH)_2$ vitamin D.

QoL and parathyroid tissue volume found at the operation and excised amount

The median volume of all parathyroids found at the operation was 9915 mm^3 (from 1939 to 71,876), with no difference observed between cases who underwent SPTx (7814 mm^3, 1939–20,320) and TPTx+AG (12,384 mm^3, 7330–71,876) (P=0.07) or between asymptomatic (11,733 mm^3, from 5194 to 16,240) and symptomatic cases (3142 mm^3, 2300–7837; P=0.4911). The median reduction of this tissue was 94% (87–95%).

There was no statistically significant correlation between the total volume and PCS (P=0.06) or MCS (P=0.33), except by inverse correlation with RP (P=0.01, r=–0.44, 95% CI=–0.70 to –0.09).

There were no significant differences of the estimated parathyroid tissue volume, the relative excised volume and of the tissue remaining in cases with or without HYPO. There was a tendency (P=0.0532; r=0.3565) and a statistically significant positive correlation (P=0.0490; r=0.3625) between PCS and remnant tissue volume at 6 and 12 months after surgery, respectively. In addition, a small statistically significant positive correlation was observed between MCS and the estimated volume of remnant of parathyroid tissue at 6 months (P=0.0380; r=0.3807), but it was not sustained at 12 months after surgery (P=0.3972; r=0.1604).

Comorbidities

At the time of PTx of the 30 patients with HPT/MEN1 studied, 18 (60%) of them had pituitary tumors (prolactinoma, 9; acromegaly, 1; non-functioning tumor, 8) being 1 case operated 2 months after PTx by non-functioning while other waited surgery for acromegaly performed more 1 year after PTx. A pancreatectomy by pancreatic NET had been performed previously in seven patients 9 months to 10 years before PTx. Also, eight patients were diabetic, five of them post-pancreatectomy and four patients had other NETs (3, bronchial; 1, thymic). Two patients had previous history of successful treatment of breast carcinoma while one patient was diagnosed with papillary thyroid carcinoma before PTx. Two patients received oncological therapy (somatostatin analog or everolimus) and had stable MEN1-related malign disease while other waited decision to begin treatment by metastasis from thymic NET.

Two patients had subtotal pancreatectomy by pancreatic NET, respectively 2 and 9 months after SPTx and the last received additionally adrenalectomy

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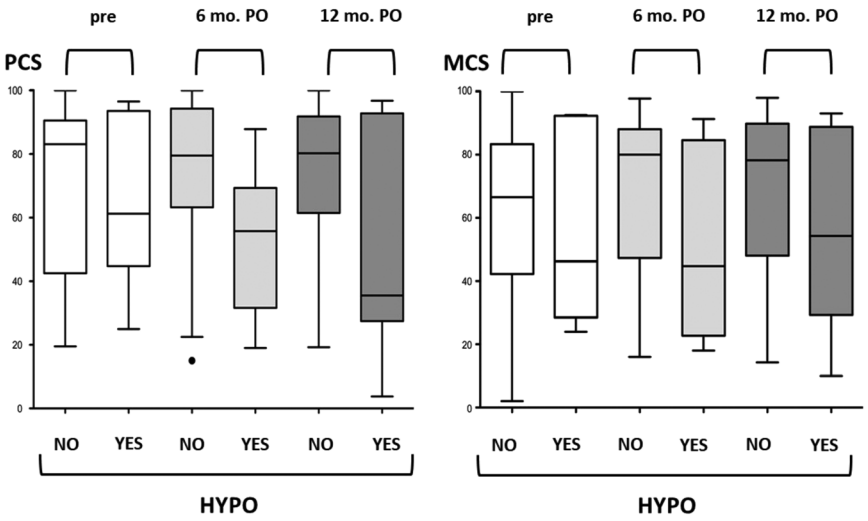

Figure 3
Postoperative changes in the median quality of life scores (PCS and MCS) according to definitive HYPO after the operation. HYPO, hypoparathyroidism; PCS, Physical Component Summary score, pre, preoperative; mo, months; MCS, Mental Component Summary score.

at the same surgical procedure for non-functioning adrenocortical tumor.

An association between comorbidities and pre- and postoperative events and with type of PTx was provided (Supplementary Table 3). Of note, all patients had at least one comorbidity. Preoperative and postoperative PCS and MCS scores of 21 patients with one to two comorbidities were compared with nine patients presenting three to four comorbidities. Worthwhile, patients with one to two comorbidities had pre-PCS (PCS $pre_{1\text{-}2}$: 88.0 (65.38–93.63) vs PCS $pre_{3\text{-}4}$: 39.50 (30–75-63-38); $P=0.0015$) and postoperative PCS better than patients with three to four comorbidities (PCS $12mo_{1\text{-}2}$: 84.5 (63.38–84.50) vs PCS $12mo_{3\text{-}4}$: 28.75 (20.25–74.13); $P=0.0031$). Also, MCS 12 months after PTx was better in cases with one to two comorbidities) MCS 12 $mo_{1\text{-}2}$: 80.25 (54.88–92.63) vs MCS 12 $mo_{3\text{-}4}$ 32.25 (16.38–83.75); $P=0.0365$) while there was a tendency to better pre-operative MCS (MCS $pre_{1\text{-}2}$: 76.50 (43.38–91.50) vs MCS $pre_{3\text{-}4}$: 46.25 (32.50–65.75); $P=0.0712$). However, there was no difference in the QoL (PCS and MCS) before and 12 months after PTx as in groups presenting one to two as in that with three to four comorbidities.

There was no statistical significance when the absence or presence of pain (mild/moderate/severe) was compared with comorbidities 1–2 and 3–4 ($P=0.2096$) or when groups with absence/mild pain or of moderate/severe pain were compared with the groups of comorbidities ($P=0.4434$).

Effect size analysis

Effect size analysis was applied to validate results of QoL (PCS and MCS) before and 12 months after PTx which were previously obtained from the non-parametric sample. This validation was conducted to the following parameters: general population (30 patients), presence/absence of preoperative symptoms, PTx type and presence/absence of HYPO.

Overall, the effect size was considered small ($r<0.3$) or moderate ($0.3<r<0.5$) to most of our results approaching QoL. Thus, our results generated from effect size ratified all previous P values. Of note, r was ≥0.5 in only two occurrences approaching PCS variation as pre- as 12 months after PTx to asymptomatic patients ($r=0.538$) or with HYPO ($r=0.639$). However, the sample size was too small, and the equality hypothesis should not be refuted.

Discussion

Overall, the QoL remained stable 1 year after PTx in 30 HPT/MEN1 of the present study contrasting with previous studies documenting gain of QoL in sporadic primary HPT (19, 20, 21, 22, 23) and renal HPT (24, 25). These different findings, probably, were modulated for diverse clinical, intra- and postoperative parameters. Of importance, preoperative QoL was negatively influenced by the occurrence of referred pain, by the presence of symptomatic HPT and advanced age. Surprisingly, postoperative QoL was not influenced by the type of selected PTx (TPTx+AG or SPTx), by the development of HYPO or by the total volume of parathyroid tissue found during surgery. In contrast, a positive correlation between the volume of remnant parathyroid tissue and QoL was noticed.

We found that preoperative symptoms and development of HYPO more frequently occurred in the elderly patients and, not surprisingly, that cases with symptomatic HPT experienced a lower QoL. Finally, we found, not previously reported by other authors that,

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the intensity of preoperative referred pain was directly associated with the occurrence of HYPO in our cohort and, as expected, with lower QoL.

Our data suggest that the negative impact of symptoms on QoL may not be explained by preoperative biochemical/hormonal findings as these parameters were similar to that found in asymptomatic cases. Most of our operated symptomatic cases were older, suggesting that they may have been more exposed to the chronic effects of PTH excess and hypercalcemia (39, 48, 49), possibly contributing to differences in QoL between symptomatic and asymptomatic cases. These data confirm recent findings reporting that some PCS parameters were worst in older MEN1 patients (32).

It has been suggested that QoL could be included as one of the criteria for PTx recommendations, based on lower QoL documented in asymptomatic sporadic HPT and its improvement in short-term randomized trials (50). Of note, a mild gain of QoL 12 months after PTx in sporadic HPT was noticed even in normocalcemic cases (51). In contrast, this gain of QoL could not be reproduced in our HPT/MEN1 data 1 year after surgery as well in asymptomatic as for symptomatic ones. Although some preoperative SF-36 domains and its summary scores (MCS and PCS) were better in our asymptomatic HPT/MEN1 cases, QoL after PTx remained stable independent of symptoms (21, 50, 52, 53). The absence of gain in QoL could have been influenced by the limited size of our casuistic and by the presence of HYPO cases remnant 1 year after PTx, a scenario not expected in sporadic HPT or even by MEN1-related comorbidities as discussed forward. Long-term follow-up of our cases may exclude the potential influence of HYPO as full recovery of parathyroid function more than 1 year after PTx in MEN1 patients has been observed (54).

As expected, measured pain by NRS correlated inversely with MCS and PCS reinforcing the strong impact of pain on QoL. Of note, some patients referred general preoperative pain independently of the presence/absence of HPT-related symptoms. It is possible that the pain complaint could be justified by other MEN1-related comorbidities resultant of tumors, surgical treatment (post-pancreatectomy diabetes, panhypopituitarism, etc.) or drug adverse effects (18). Also, body pain may be part of the anxious and depressive symptoms impacting QoL. Furthermore, MEN1 patients have worse QoL, more anxiety, depression and fatigue when compared with sporadic HPT or other chronic conditions (28, 30, 31). By its complexity, QoL in HPT/MEN1 patients may be strongly influenced by synchronic occurrence of other MEN1-related tumors and their comorbidities. Thus, it is not possible to exclude the influence of multiple comorbidities in the absence of gain of QoL in our cohort 1 year after PTx, commonly seen in sporadic forms of HPT.

Of value, all preoperative (age at the surgery, biochemical/hormonal values and QoL scores) and intraoperative (total volume of parathyroid glands identified, excised or remnant) parameters were similar independent of the eligible surgical approach (PTxT+AG or SPTx). These homogeneous data strengthen the comparative analysis of the surgical groups although they have not been randomized. The present analysis was performed at 12 months after PTx to minimize potential interference of higher frequency of HYPO after TPTx+AG as of hungry bone syndrome expected at 6 months (54). Thus, we document no impact of the surgical type on QoL after 12 months independently if patients have developed HYPO or not.

Importantly, five (SPTx, 4; TPTx+AG, 1) out of seven patients with HYPO at 12 months had normal values of PTH after this period requiring suspension of reposition therapy. It is expected that this potential interference of HYPO on QoL may be minimized as these patients may gain functionality of the tissue left in the neck or autografted during long-term follow-up. In fact, some autografts may take 4 years to present adequate function (55). It is possible that the tissue functionality of the stump or autograft is more important than the type of surgery chosen considering that the remnant parathyroid volume was similar in these surgical techniques and in cases with or without HYPO. We understand that a more accurate standardization of remnant volume associated with recent studies investigating intraoperative vascular vitality of the parathyroid tissue with indocyanine green fluorescence may contribute to estimate the functionality of the stump (56). In opposite, the fear of higher risk of HYPO after TPTx+AG (14) requires future studies to investigate potential predictors of functionality. The adoption of similar volume of remnant tissue to stump and autograft did not result in higher risk of HYPO in cases submitted to TPTx+AG. However, further studies addressing larger cohorts are awaited.

Of value, Goswani et al (18) noticed that the surgical cure of HPT self-reported by MEN1 patients answering a questionnaire on a web-based platform was significantly associated with improved QoL independently of frequency and of when PTx was performed or of hypocalcemia. However, in this cross-sectional study, biochemical/hormonal data about calcium metabolism are not revealed and the temporal relation between PTx and self-reported

information of cure is unknown. Thus, the asymptomatic occurrence of cases with mild HYPO or recurrent HPT may not be excluded and the impact of the successful treatment of the MEN1-related multiple comorbidities should have influenced this gain of QoL.

Interestingly, the preoperative pain perception was statistically related with the occurrence of HYPO as it was more prevalent and intense in the group which developed HYPO contrasting with stability in group without HYPO. This role as a predictive factor would be reinforced by the absence of differences in preoperative QoL and biochemical features in groups with and without HYPO. This correlation could be explained, at least in part, by the presence of other MEN1-related comorbidities potentially influencing the perception of general preoperative pain. In fact, the preoperative pain may disclose more sensitive patients due to multiple comorbidities that could be less capable to tolerate some nonspecific symptoms or even mild hypocalcemia requiring higher doses of calcium to restore normal values of calcemia. However, the small number of cases to support correlations between comorbidities, preoperative pain and HYPO prevented us to validate this hypothesis.

Considering recent studies documenting a milder phenotype, better outcome and longer survival of MEN1 phenocopies than observed in *MEN1* carriers, studies of QoL should support full genetic testing to distinguish these subgroups. To our knowledge, only two papers clearly excluded phenocopies (29, 30). Importantly, all 30 cases of the present study had a pathogenic *MEN1* germline variant identified by Sanger or MLPA assay nullifying potential interferences on QoL for phenocopies.

Multifactorial influences resulted in stable QoL 1 year after PTx in our 30 HPT/MEN1 cases. This apparent global stability of the QoL scores documented, independently of type of performed PTx and presence/absence of HYPO, should not frustrate expectance or discourage clinics and surgeons for indication of PTx. On the contrary, most patients will have potential benefits after restored normocalcemia avoiding or minimizing short and long-term HPT-related complications on target organs without additional impact on QoL in this complex disorder (3, 9, 32, 39, 48, 49, 57). Thus, multifactorial influences seem to be more relevant for modulating QoL in MEN1 than only PTx-related technical aspects. Other prospective QoL studies in larger HPT/MEN1 series with longer follow-up periods after PTx are warranted to confirm present findings, amplifying our knowledge on this subject and, potentially, refining the decisions making in upfront of surgical treatment of HPT/MEN1 and clinical management.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-22-0021.

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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Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

Author contribution statement

F L M Montenegro and D M Lourenço Junior: contributed equally.

References

1 Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F, Brandi ML, *et al.* Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 2990–3011. (https://doi.org/10.1210/jc.2012-1230)

2 Brandi ML, Agarwal SK, Perrier ND, Lines KE, Valk GD & Thakker RV. Multiple endocrine neoplasia type 1: latest insights. *Endocrine Reviews* 2021 **42** 133–170. (https://doi.org/10.1210/endrev/bnaa031)

3 Lourenço Jr DM, Toledo RA, Mackowiak II, Coutinho FL, Cavalcanti MG, Correia-Deur JE, Montenegro F, Siqueira SA, Margarido LC, Machado MC, *et al.* Multiple endocrine neoplasia type 1 in Brazil: MEN1 founding mutation, clinical features, and bone mineral density profile. *European Journal of Endocrinology* 2008 **159** 259–274. (https://doi.org/10.1530/EJE-08-0153)

4 Toledo SP, Lourenço Jr DM & Toledo RA. A differential diagnosis of inherited endocrine tumors and their tumor counterparts. *Clinics* 2013 **68** 1039–1056. (https://doi.org/10.6061/clinics/2013(07)24)

5 Kamilaris CDC & Stratakis CA. Multiple endocrine neoplasia type 1 (MEN1): an update and the significance of early genetic and clinical diagnosis. *Frontiers in Endocrinology* 2019 **10** 339. (https://doi.org/10.3389/fendo.2019.00339)

6 Bassett JH, Forbes SA, Pannett AA, Lloyd SE, Christie PT, Wooding C, Harding B, Besser GM, Edwards CR, Monson JP, *et al.* Characterization of mutations in patients with multiple endocrine neoplasia type 1. *American Journal of Human Genetics* 1998 **62** 232–244. (https://doi.org/10.1086/301729)

7 Vergès B, Boureille F, Goudet P, Murat A, Beckers A, Sassolas G, Cougard P, Chambe B, Montvernay C & Calender A. Pituitary disease in MEN type 1 (MEN1): data from the France-Belgium MEN1 multicenter study. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 457–465. (https://doi.org/10.1210/jcem.87.2.8145)

8 Goudet P, Dalac A, Le Bras M, Cardot-Bauters C, Niccoli P, Lévy-Bohbot N, du Boullay H, Bertagna X, Ruszniewski P, Borson-Chazot F, *et al.* MEN1 disease occurring before 21 years old: a 160-patient cohort study from the Groupe d'étude des Tumeurs Endocrines. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 1568–1577. (https://doi.org/10.1210/jc.2014-3659)

9 Vannucci L, Marini F, Giusti F, Ciuffi S, Tonelli F & Brandi ML. MEN1 in children and adolescents: data from patients of a regional referral center for hereditary endocrine tumors. *Endocrine* 2018 **59** 438–448. (https://doi.org/10.1007/s12020-017-1322-5)

10 Lourenço Jr DM, Toledo RA, Coutinho FL, Margarido LC, Siqueira SA, dos Santos MA, Montenegro FL, Machado MC & Toledo SP. The impact of clinical and genetic screenings on the management of the multiple endocrine neoplasia type 1. *Clinics* 2007 **62** 465–476. (https://doi.org/10.1590/S1807-59322007000400014)

11 Marini F, Giusti F, Tonelli F & Brandi ML. When parathyroidectomy should be indicated or postponed in adolescents with MEN1-related primary hyperparathyroidism. *Frontiers in Endocrinology* 2018 **9** 597. (https://doi.org/10.3389/fendo.2018.00597)

12 Giusti F, Tonelli F & Brandi ML. Primary hyperparathyroidism in multiple endocrine neoplasia type 1: when to perform surgery? *Clinics* 2012 **67** (Supplement 1) 141–144. (https://doi.org/10.6061/clinics/2012(sup01)23)

13 Montenegro FLM, Brescia MDG, Lourenço DM, Arap SS, d'Alessandro AF, de Britto E Silva Filho G & Toledo SPA. Could the less-than subtotal parathyroidectomy be an option for treating young patients with multiple endocrine neoplasia type 1-related hyperparathyroidism? *Frontiers in Endocrinology* 2019 **10** 123. (https://doi.org/10.3389/fendo.2019.00123)

14 Tonelli F, Giudici F, Cavalli T & Brandi ML. Surgical approach in patients with hyperparathyroidism in multiple endocrine neoplasia type 1: total versus partial parathyroidectomy. *Clinics* 2012 **67** (Supplement 1) 155–160. (https://doi.org/10.6061/clinics/2012(sup01)26)

15 Moffett JM & Sulibur J. Parathyroid autotransplantation. *Endocrine Practice* 2011 **17** (Supplement 1) 83–89. (https://doi.org/10.4158/EP10377.RA)

16 Orloff LA, Wiseman SM, Bernet VJ, Fahey TJ, Shaha AR, Shindo ML, Snyder SK, Stack Jr BC, Sunwoo JB & Wang MB. American Thyroid Association statement on postoperative hypoparathyroidism: diagnosis, prevention, and management in adults. *Thyroid* 2018 **28** 830–841. (https://doi.org/10.1089/thy.2017.0309)

17 Clarke BL, Brown EM, Collins MT, Jüppner H, Lakatos P, Levine MA, Mannstadt MM, Bilezikian JP, Romanischen AF & Thakker RV. Epidemiology and diagnosis of hypoparathyroidism. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 2284–2299. (https://doi.org/10.1210/jc.2015-3908)

18 Goswami S, Peipert BJ, Helenowski I, Yount SE & Sturgeon C. Disease and treatment factors associated with lower quality of life scores in adults with multiple endocrine neoplasia type I. *Surgery* 2017 **162** 1270–1277. (https://doi.org/10.1016/j.surg.2017.07.023)

19 Weber T, Keller M, Hense I, Pietsch A, Hinz U, Schilling T, Nawroth P, Klar E & Buchler MW. Effect of parathyroidectomy on quality of life and neuropsychological symptoms in primary hyperparathyroidism. *World Journal of Surgery* 2007 **31** 1202–1209. (https://doi.org/10.1007/s00268-007-9006-6)

20 Caillard C, Sebag F, Mathonnet M, Gibelin H, Brunaud L, Loudot C, Kraimps JL, Hamy A, Bresler L, Charbonnel B, *et al.* Prospective evaluation of quality of life (SF536v2) and nonspecific symptoms before and after cure of primary hyperparathyroidism (1-year follow-up). *Surgery* 2007 **141** 153–159; discussion 159. (https://doi.org/10.1016/j.surg.2006.12.004)

21 Bollerslev J, Jansson S, Mollerup CL, Nordenstrom J, Lundgren E, Tørring O, Varhaug JE, Baranowski M, Aanderud S, Franco C, *et al.* Medical observation, compared with parathyroidectomy, for asymptomatic primary hyperparathyroidism: a prospective randomized trial. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 1687–1692. (https://doi.org/10.1210/jc.2006-1836)

22 Brito K, Edirimanne S & Eslick GD. The extent of improvement of health-related quality of life as assessed by the SF36 and Paseika scales after parathyroidectomy in patients with primary hyperparathyroidism – a systematic review and meta-analysis. *International Journal of Surgery* 2015 **13** 245–249. (https://doi.org/10.1016/j.ijsu.2014.12.004)

23 Cheng SP, Lee JJ, Liu TP, Yang PS, Liu SC, Hsu YC & Liu CL. Quality of life after surgery or surveillance for asymptomatic primary hyperparathyroidism: a meta-analysis of randomized controlled trials. *Medicine* 2015 **94** e931. (https://doi.org/10.1097/MD.0000000000000931)

24 Packman KS & Demeure MJ. Indications for parathyroidectomy and extent of treatment for patients with secondary hyperparathyroidism. *Surgical Clinics of North America* 1995 **75** 465–482. (https://doi.org/10.1016/s0039-6109(16)46634-x)

25 Filho WA, van der Plas WY, Brescia MDG, Nascimento Jr CP, Goldenstein PT, Neto LMM, Arap SS, Custodio MR, Bueno RO, Moyses RMA, *et al.* Quality of life after surgery in secondary hyperparathyroidism, comparing subtotal parathyroidectomy with total parathyroidectomy with immediate parathyroid autograft: prospective randomized trial. *Surgery* 2018 **164** 978–985. (https://doi.org/10.1016/j.surg.2018.06.032)

26 You YN, Thompson GB, Young Jr WF, Larson D, Farley DR, Richards M & Grant CS. Pancreatoduodenal surgery in patients with multiple endocrine neoplasia type 1: operative outcomes, long-term function, and quality of life. *Surgery* 2007 **142** 829–836; discussion 836.e1. (https://doi.org/10.1016/j.surg.2007.09.010)

27 Peipert BJ, Goswami S, Helenowski I, Yount SE & Sturgeon C. Financial burden is associated with worse health-related quality of life in adults with multiple endocrine neoplasia type 1. *Surgery* 2017 **162** 1278–1285. (https://doi.org/10.1016/j.surg.2017.07.010)

28 Peipert BJ, Goswami S, Yount SE & Sturgeon C. Health-related quality of life in MEN1 patients compared with other chronic conditions and the United States general population. *Surgery* 2018 **163** 205–211. (https://doi.org/10.1016/j.surg.2017.04.030)

29 van Leeuwaarde RS, Pieterman CRC, Bleiker EMA, Dekkers OM, van der Horst-Schrivers AN, Hermus AR, de Herder WW, Drent ML, Bisschop PH, Havekes B, *et al.* High fear of disease occurrence is associated with low quality of life in patients with multiple endocrine neoplasia type 1: results from the Dutch MEN1 study group. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 2354–2361. (https://doi.org/10.1210/jc.2018-00259)

30 van Leeuwaarde RS, Pieterman CRC, May AM, Dekkers OM, van der Horst-Schrivers AN, Hermus AR, de Herder WW, Drent ML, Bisschop PH, Havekes B, *et al.* Health-related quality of life in patients with multiple endocrine neoplasia type 1. *Neuroendocrinology* 2021 **111** 288–296. (https://doi.org/10.1159/000508374)

31 Berglund G, Lidén A, Hansson MG, Oberg K, Sjöden PO & Nordin K. Quality of life in patients with multiple endocrine neoplasia type 1 (MEN 1). *Familial Cancer* 2003 **2** 27–33. Erratum in: *Familial Cancer* 2003 **2** 151. (https://doi.org/10.1023/A:1023252107120)

32 Giusti F, Cioppi F, Fossi C, Marini F, Masi L, Tonelli F & Brandi ML. Quality of life in Italian patients with multiple endocrine neoplasia type 1 (MEN 1): results of an extensive survey. *Orphanet Journal of Rare Diseases* 2021 **16** 16. (https://doi.org/10.1186/s13023-020-01650-y)

33 van Beek DJ, van Leeuwaarde RS, Pieterman CR, Vriens MR & Valk GD. Quality in, quality out, a stepwise approach to EBM for rare diseases promoted by MEN1. *Endocrine Connections* 2018 **7** R260–R274. (https://doi.org/10.1530/EC-18-0359)

34 Pieterman CRC, Hyde SM, Wu SY, Landry JP, Chiang YJ, Christakis I, Grubbs EG, Fisher SB, Graham PH, Waguespack SG, *et al.* Understanding the clinical course of genotype-negative MEN1 patients can inform management strategies. *Surgery* 2021 **169** 175–184. (https://doi.org/10.1016/j.surg.2020.04.067)

35 Carvalho RA, Urtremari B, Jorge AAL, Santana LS, Quedas EPS, Sekiya T, Longuini VC, Montenegro FLM, Lerario AM, Toledo SPA, *et al.* Germline mutation landscape of multiple endocrine neoplasia type 1 using full gene next-generation sequencing. *European Journal of Endocrinology* 2018 **179** 391–407. (https://doi.org/10.1530/EJE-18-0430)

36 Toledo RA, Lourenço Jr DM, Coutinho FL, Quedas E, Mackowiack I, Machado MC, Montenegro F, Cunha-Neto MB, Liberman B, Pereira MA, *et al*. Novel MEN1 germline mutations in Brazilian families with multiple endocrine neoplasia type 1. *Clinical Endocrinology* 2007 **67** 377–384. (https://doi.org/10.1111/j.1365-2265.2007.02895.x)

37 Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C & Potts Jr JT. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 3561–3569. (https://doi.org/10.1210/jc.2014-1413)

38 Norton JA, Venzon DJ, Berna MJ, Alexander HR, Fraker DL, Libutti SK, Marx SJ, Gibril F & Jensen RT. Prospective study of surgery for primary hyperparathyroidism (HPT) in multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: long-term outcome of a more virulent form of HPT. *Annals of Surgery* 2008 **247** 501–510. (https://doi.org/10.1097/SLA.0b013e31815efda5)

39 Lourenço Jr DM, Coutinho FL, Toledo RA, Montenegro FL, Correia-Deur JE & Toledo SP. Early-onset, progressive, frequent, extensive, and severe bone mineral and renal complications in multiple endocrine neoplasia type 1-associated primary hyperparathyroidism. *Journal of Bone and Mineral Research* 2010 **25** 2382–2391. (https://doi.org/10.1002/jbmr.125)

40 Montenegro FLM, Neves MC, Lourenço Jr DM, Arap SS, Nascimento Jr CP, Toledo SPA, Brandao LG & Cordeiro AC. Thymectomy in the surgical approach to hyperparathyroidism in type 1 multiple endocrine neoplasia. *Revista Brasileira de Cirurgia da Cabeça e Pescoço* 2010 **39** 174–178.

41 Al-Salameh A, Cadiot G, Calender A, Goudet P & Chanson P. Clinical aspects of multiple endocrine neoplasia type 1. *Nature Reviews: Endocrinology* 2021 **17** 207–224. (https://doi.org/10.1038/s41574-021-00468-3)

42 Brazier JE, Harper R, Jones NMB, O'Cathain A, Thomas KJ, Usherwood T & Westlake L. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992 **305** 160–164. (https://doi.org/10.1136/bmj.305.6846.160)

43 Ware Jr JE & Gandek B. Overview of the SF-36 health survey and the international quality of life assessment (IQOLA) project. *Journal of Clinical Epidemiology* 1998 **51** 903–912. (https://doi.org/10.1016/s0895-4356(98)00081-x)

44 van der Plas WY, Dulfer RR, Engelsman AF, Vogt L, de Borst MH, van Ginhoven TM, Kruijff S & Dutch Hyperparathryoid Study Group (DHSG). Effect of parathyroidectomy and Cinacalcet on quality of life in patients with end-stage renal disease-related hyperparathyroidism: a systematic review. *Nephrology, Dialysis, Transplantation* 2017 **32** 1902–1908. (https://doi.org/10.1093/ndt/gfx044)

45 Erez G, Selman L & Murtagh FE. Measuring health-related quality of life in patients with conservatively managed stage 5 chronic kidney disease: limitations of the Medical Outcomes Study Short Form 36: SF-36. *Quality of Life Research* 2016 **25** 2799–2809. (https://doi.org/10.1007/s11136-016-1313-7)

46 Steenbeek ED, Ramspek CL, van Diepen M, Dekker FW & Achterberg WP. The association between pain perception and care dependency in older nursing home residents: a prospective cohort study. *Journal of the American Medical Directors Association* 2020 **22** 676–681. (https://doi.org/10.1016/j.jamda.2020.07.022)

47 Jensen MP, Smith DG, Ehde DM & Robinsin LR. Pain site and the effects of amputation pain: further clarification of the meaning of mild, moderate, and severe pain. *Pain* 2001 **91** 317–322. (https://doi.org/10.1016/S0304-3959(00)00459-0)

48 Burgess JR, Greenaway TM & Shepherd JJ. Expression of the MEN-1 gene in a large kindred with multiple endocrine neoplasia type 1. *Journal of Internal Medicine* 1998 **243** 465–470. (https://doi.org/10.1046/j.1365-2796.1998.00275.x)

49 Eller-Vainicher C, Chiodini I, Battista C, Viti R, Mascia ML, Massironi S, Peracchi M, D'Agruma L, Minisola S, Corbetta S, *et al*. Sporadic and MEN1-related primary hyperparathyroidism: differences in clinical expression and severity. *Journal of Bone and Mineral Research* 2009 **24** 1404–1410. (https://doi.org/10.1359/jbmr.090304)

50 Walker MD & Silverberg SJ. Quality of life in primary hyperparathyroidism revisited: keep calm and carry on? *Journal of Bone and Mineral Research* 2021 **36** 1–2. (https://doi.org/10.1002/jbmr.4225)

51 Bannani S, Christou N, Guérin C, Hamy A, Sebag F, Mathonnet M, Guillot P, Caillard C, Blanchard C & Mirallié E. Effect of parathyroidectomy on quality of life and non-specific symptoms in normocalcaemic primary hyperparathyroidism. *British Journal of Surgery* 2018 **105** 223–229. (https://doi.org/10.1002/bjs.10739)

52 Rao DS, Phillips ER, Divine GW & Talpos GB. Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 5415–5422. (https://doi.org/10.1210/jc.2004-0028)

53 Ambrogini E, Cetani F, Cianferotti L, Vignali E, Banti C, Viccica G, Oppo A, Miccoli P, Berti P, Bilezikian JP, *et al*. Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 3114–3121. (https://doi.org/10.1210/jc.2007-0219)

54 Coutinho FL, Lourenco Jr DM, Toledo RA, Montenegro FL & Toledo SP. Post-surgical follow-up of primary hyperparathyroidism associated with multiple endocrine neoplasia type 1. *Clinics* 2012 **67** (Supplement 1) 169–172. (https://doi.org/10.6061/clinics/2012(sup01)28)

55 Lambert LA, Shapiro SE, Lee JE, Perrier ND, Truong M, Wallace MJ, Hoff AO, Gagel RF & Evans DB. Surgical treatment of hyperparathyroidism in patients with multiple endocrine neoplasia type 1. *Archives of Surgery* 2005 **140** 374–382. (https://doi.org/10.1001/archsurg.140.4.374)

56 Kim DH, Kim SH, Jung J, Kim SW & Hwang SH. Indocyanine green fluorescence for parathyroid gland identification and function prediction: systematic review and meta-analysis. *Head and Neck* 2022 **44** 783–791. (https://doi.org/10.1002/hed.26950)

57 Lourenço Jr DM, Coutinho FL, Toledo RA, Gonçalves TD, Montenegro FL & Toledo SP. Biochemical, bone and renal patterns in hyperparathyroidism associated with multiple endocrine neoplasia type 1. *Clinics* 2012 **67** (Supplement 1) 99–108. (https://doi.org/10.6061/clinics/2012(sup01)17)

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