Clinical profile and quality of life scores in Chronic Hypoparathyroidism: a transversal retrospective study

Perfil clínico e escores de qualidade de vida no Hipoparatireoidismo Crônico: um estudo retrospectivo transversal

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ABSTRACT
Introduction: In patients with hypoparathyroidism, conventional therapy maintains parathyroid hormone (PTH)-dependent mineral metabolism homeostasis but is unable to prevent emergence of comorbidities and low quality of life. Objectives: To evaluate long-term progression of patients with hypoparathyroidism receiving conventional therapy and their quality of life compared with patients with primary hypothyroidism and healthy controls. Design and Setting: Retrospective cohort study for quality-of-life analysis and transversal cut on clinical profile. Patients with hypoparathyroidism from four public referral centers in endocrinology and bone metabolism in the metropolitan region of Rio de Janeiro. Material and Methods: Quality of life by SF-36 protocol, and clinical profile by medical record analysis. Results: 243 individuals with hypoparathyroidism (n=113), hypothyroidism (n=65), and healthy controls (n=65) included. Median time since diagnosis and duration of conventional therapy was 8 years (IQR 4–17 years). Data on type of conventional therapy (median, minimum–maximum daily dose, percentage of patients with hypoparathyroidism using each medication): calcium supplementation (2000 mg/day, 200–6000 mg/day, 95%), cholecalciferol (2000 IU/day, 200–40000 IU/day, 44%), calcitriol (0.5 μg/day, 0.25–2 μg/day, 77%), thiazides (25 mg/day, 12.5–100 mg/day, 44%). Conclusions: Conventional therapy is associated with homeostasis of serum mineral levels, but not with improved quality of life. Compared to patients with hypothyroidism, those with additional hypoparathyroidism had lower scores in six SF-36 domains. Conventional therapy successfully maintained normal calcium levels with often high doses of calcium, vitamin D, and thiazides but could not prevent low quality of life scores and comorbidities.

Keywords: disorders of Calcium/Phosphate, quality of life, Hypoparathyroidism, PTH, Vitamin D.

RESUMO
Introdução: Em pacientes com hipoparatireoidismo, a terapia convencional mantém homeostase do metabolismo mineral dependente do hormônio paratireoidiano (PTH), mas é incapaz de evitar o surgimento de comorbidades e baixa qualidade de vida. Objetivos: Avaliar a progressão a longo prazo de pacientes com hipoparatireoidismo recebendo terapia convencional e sua qualidade de vida em comparação com pacientes com hipotireoidismo primário e controles saudáveis. Desenho e ajuste: Estudo de coorte retrospectivo para análise da qualidade de vida e corte transversal no perfil clínico. Pacientes com hipoparatireoidismo de quatro centros públicos de referência em endocrinologia e metabolismo ósseo na região metropolitana do Rio de Janeiro. Material e Métodos: Qualidade de vida pelo protocolo SF-36, e perfil clínico pela análise de prontuários médicos. Resultados: 243 indivíduos com hipoparatireoidismo (n=113), hipotireoidismo (n=65), e controles saudáveis (n=65) incluídos.

O tempo médio desde o diagnóstico e duração da terapia convencional foi de 8 anos (IQR 4-17 anos). Dados sobre o tipo de terapia convencional (mediana, dose mínima-máxima diária, porcentagem de pacientes com hipoparatireoidismo usando cada medicamento): suplementação de cálcio (2000 mg/dia, 200-6000 mg/dia, 95%), colecalciferol (2000 IU/dia, 200-40000 IU/dia, 44%), calcitriol (0,5 μg/dia, 0,25-2 μg/dia, 77%), tiazidas (25 mg/dia, 12,5-100 mg/dia, 44%). Conclusões: A terapia convencional está associada à homeostase dos níveis séricos de minerais, mas não à melhoria da qualidade de vida. Em comparação com pacientes com hipotireoidismo, aqueles com hipoparatireoidismo adicional tiveram escores mais baixos em seis domínios SF-36. A terapia convencional manteve com sucesso os níveis normais de cálcio com doses frequentemente altas de cálcio, vitamina D e tiazidas, mas não conseguiu evitar escores baixos de qualidade de vida e comorbidades.

Palavras-chave: desordens de Cálcio/Fosfato, qualidade de vida, Hipoparatireoidismo, PTH, Vitamina D.

1 INTRODUCTION

Hypoparathyroidism is a rare endocrine disorder characterized by hypocalcemia due to insufficient secretion of PTH. The most frequent etiology is surgical removal or loss of viability of parathyroid glands. Additionally, hypoparathyroidism can be due to autoimmune, metabolic, infiltrative, or genetic disorders[1,2]. The diagnosis is made in the context of low serum ionized or albumin-corrected calcium concentration and inappropriately low or undetectable levels of PTH[3, 4].

Until recently, hypoparathyroidism was the last classic endocrine deficiency for which the synthetic hormone was not approved for replacement therapy[5]. In Brazil, we still do not have access to rhPTH[1–84]. Due to a lack of definitive therapeutic solutions for hypoparathyroidism, the conventional treatment for this condition includes control of symptoms with increased dietary calcium intake and administration of calcium and vitamin D (analogues or calcitriol), in addition to occasional thiazide diuretics. However, even when properly administered, conventional therapy appears to be unable to prevent comorbidities[5, 6].

PTH is a major regulator of calcium and phosphate homeostasis, and the consequences of hypoparathyroidism are related to the imbalance in the metabolism of calcium and phosphorus due to the loss of the biological action of PTH [3]. In a long-term scenario, this disease can affect several systems and tissues, causing important cardiovascular, neurological, neuropsychiatric, renal, muscular and bone consequences[4].

Additionally, studies have shown that patients with hypoparathyroidism have low quality of life (QoL)[7, 8]. However, the nature of this impairment and its relationship to biochemical control or other aspects of the disease are not well characterized[4].

This study was performed to describe the clinical profile and quality-of-life in patients with hypoparathyroidism receiving conventional therapy and comparing to endocrinology and bone metabolism units at public tertiary health care centers located in the metropolitan region of the city of Rio de Janeiro.

2 MATERIAL AND METHODS

2.1 STUDY DESIGN AND PATIENT SELECTION

In this transversal retrospective study, we selected adult patients diagnosed with hypoparathyroidism (HP) for more than 12 months who were receiving conventional treatment (CT) and were followed up at four tertiary public health centers, references in endocrinology and bone metabolism, located in the metropolitan region of Rio de Janeiro. The sample was determined by convenience. We excluded patients with hypoparathyroidism developed after parathyroidectomy for treatment of hyperparathyroidism secondary or tertiary to chronic kidney disease. Given that our patients, in addition to HP, also had post-surgical hypothyroidism (HT), we chose to assess the QoL scores of a group of individuals with HT, as well as a group of healthy controls (HC) and therefore to better adjust the comparison of the QoL scores.

The study was approved by the research ethics committees of all participating centers. The CAAE number was 82845317.0.0000.5243. Before enrollment, all participants signed a free and informed consent form. Participants were enrolled and completed the SF-36 questionnaire between April 2018 and March 2020.

2.2 DATA COLLECTION

Information was obtained from the patients' medical records at the time of diagnosis (T1 period), during the entire follow-up and subsequently related to an interview at the most recent consultation (T2 period). The information collected included the presence of preexisting diseases, comorbidities developed during follow up, use of medications, and epidemiological, clinical, and laboratory data.

2.3 ANALYSIS OF QUALITY OF LIFE

Quality of life was evaluated in a cross-section analysis during the T2 period using the 36-item Medical Outcomes Short-Form Health Survey (SF-36)[9] validated in the Brazilian population[10]. The SF-36 is a generic instrument for evaluation of quality of life, which is shorter than other instruments and easy to understand and apply. This survey comprises 36 questions

across eight domains, namely, physical functioning, physical role limitations, pain, general health, vitality, social functioning, emotional role limitations, and mental health. The SF-36 scores range from 0 to 100, in which 0 and 100 correspond to the worst and best general health status, respectively.

2.4 STATISTICAL ANALYSIS

We analyzed the data using the R statistical package (The R Foundation for Statistical Computing, Vienna, Austria)[11]. For descriptive and qualitative analysis, we used frequencies and percentages, and for quantitative variables, we used mean and interquartile range (IQR) values. Normal distribution data were analyzed with Student's t test. For correlations between numeric variables, we used Pearson's or Spearman's correlation test. The results were compared in two ways. We used the Mann-Whitney test for comparisons between two groups (HP+HT versus HT and HP+HT versus HC) and the Kruskal-Wallis test for comparisons between three groups (QoL analysis). For correlations between clinical data in patients with hypoparathyroidism and the SF-36 domains, we used the Spearman's test. We adopted a significance level of 5% in all tests.

3 RESULTS

A total of 194 individuals agreed to participate in the study. In all, 64 patients had HP, who also presented controlled postsurgical HT and completed the SF-36 survey. We also included 65 healthy controls and 65 controls with HT to compare their QoL scores with those in the group of patients with HP + HT.

Among the 64 patients with HP, 60 were women. The median duration of diagnosis and conventional treatment was 7 years (IQR 3 – 13.25 years). The median of serum PTH levels was 3.6 pg/mL (IQR 3 – 9.3 pg/mL) at the diagnosis (T1), and 5.4 pg/mL (IQR 3 – 11.3 pg/mL) at the most recent consultation (T2). The indications for surgery in these patients were nontoxic multinodular goiter (n = 38, 59.4%), thyroid cancer (n = 13, 20.3%), Graves' disease (n = 7, 10.9%), and toxic nodular/multinodular goiter (n = 3, 4.7%), others or unknown (5%).

Collected and analyzed data show that only serum calcium and serum phosphorus were significantly different between T1 and T2. Other data were different but did not show statistical significance after the T test. Table 1 shows this data and the profile of the patients with HP+HT.

Table 1. Profile of patients with hypoparathyroidism receiving conventional treatment (mean ± standard deviation [SD] or minimum–maximum [min-max] values), n = 64.

	T1	T2
Data		
Age (years)	46.25 ± 15.84	56.33 ± 14.89
Weight (kg)	72.71 ± 18.50	75.01 ± 17.13
Height (m)	1.60 ± 0.10	1.59 ± 0.08
BMI (kg/m²)	28.45 ± 5.69	29.16 ± 5.24
Serum calcium (mg/dL)	6.98 ± 1.42	8.29 ± 0.79[#]
Serum phosphorus (mg/dL)	5.22 ± 1.28	4.66 ± 0.82[*]
Serum magnesium (mg/dL)	1.70 ± 0.27	1.87 ± 0.45
Urinary calcium (mg/24h)	155.80 ± 121.44	183.67 ± 237.69
Calcium x phosphorus product	35.88 ± 8.71	38.23 ± 6.58
Urinary calcium (mg/kg/24h)	2.12 ± 1.64	2.29 ± 1.82
Serum 25OHD (ng/mL)	51.91 ± 58.02	49.22 ± 39.62
Serum creatinine	0.79 ± 0.19	0.85 ± 0.20

T1: diagnosis; T2: most recent appointment. *p=0.005; [#]p<0.0001. Abbreviations – BMI: body mass index; 25OHD: 25-hydroxyvitamin D.

The CT observed in T2 included elementary calcium (n = 62) with median dose 2000 mg/day; calcitriol (n = 48), with median dose 0.5 µg/day; cholecalciferol (n = 33), with median dose 1600 IU/day; and thiazides (n = 31), with median dose 25 mg/day. This data and common association of cholecalciferol and calcitriol are shown in Tables 1 and 2.

Table 2. Medications used in conventional treatment of 64 patients with chronic hypoparathyroidism.

Medications in use	**Median**	**Min – Max**	**n (%)**
Elemental calcium (mg/day)	2000	500 – 6000	62 (97)
Calcitriol (µg/day) [a]	1600[a]	400 – 40000[c]	22 (34)
Cholecalciferol (IU/day) [b]	0.5[b]	0.25 – 2.00 [d]	7 (11)
Thiazides (mg/day)	25	12.5 – 75	31 (48)
Calcitriol+ Cholecalciferol	a/b	c/d	26 (41)

Abbreviation – n: number of patients. The same patient may have received more than one medication.

Quality of life scores were significantly worse in patients with combined HP+HT when compared with those with HT alone or healthy controls, highlighting the scores of physical role limitations and general health that were the worst of the three groups. The other scores that were significantly different and worse in HT+HP group were physical functioning, emotional

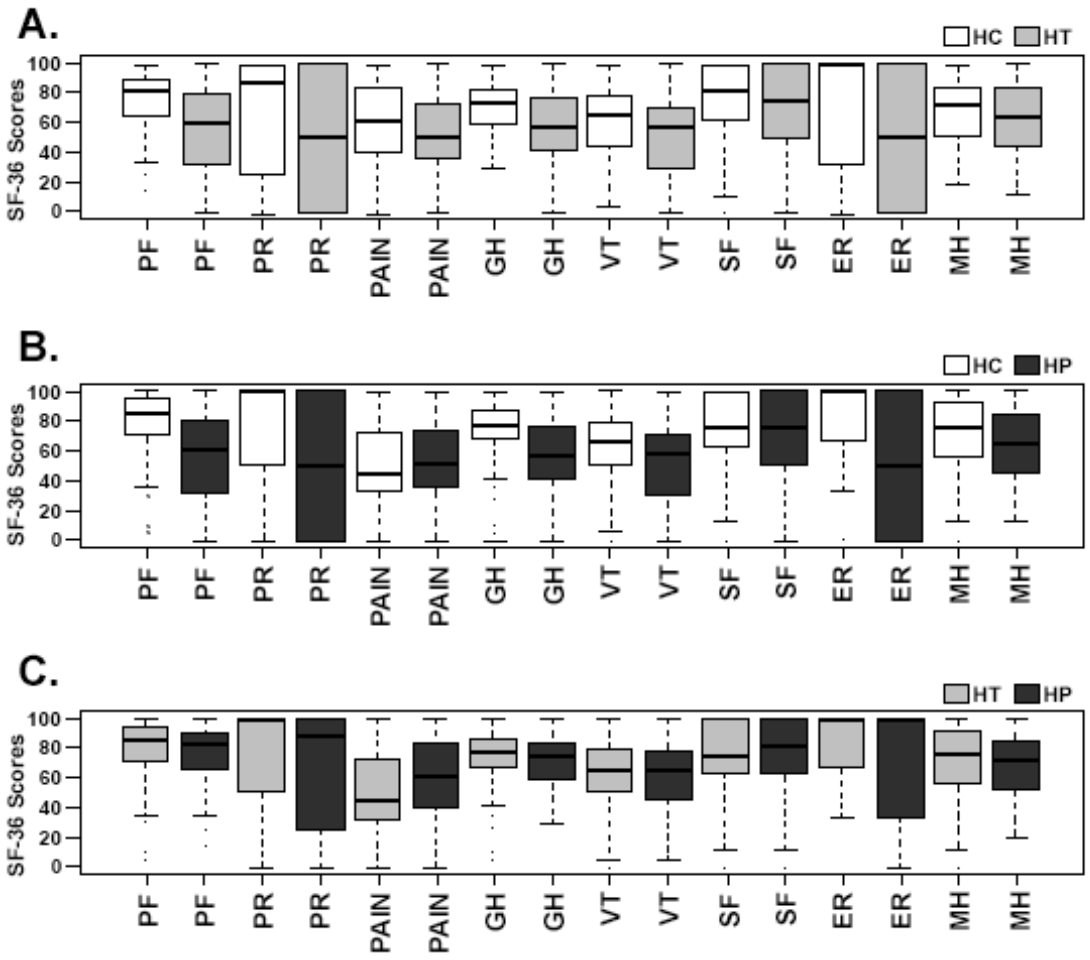
role limitations and mental health. All the tests were performed with significance level in 5%, and the tests achieved $p < 0.05$. The QoL data are shown in Table 3 and Figure 1, while the comparative analysis between groups is shown in Figure 1. Patients with HP had cataract (4.69%) and nephrolithiasis (6.25%). The analyzed data on comorbidities that emerged after the diagnosis of chronic hypoparathyroidism and during conventional treatment are shown in Table 4. Among patients with HP+HT, age showed no correlation with QoL scores. Significant correlations between the profile categories and the SF-36 domains are shown in Table 5.

Table 3. Results of the 36-item Medical Outcomes Short-Form Health Survey (SF-36) completed by patients with hypoparathyroidism receiving conventional treatment, mean (± standard deviation [SD]).

Category (scores)	HC	HT	HP + HT
n/(W)	65 (63)	65 (60)	64 (60)
Age	52.51± 13.86	59.30 ± 11.31	57.08 ± 14.78
Physical functioning*	79.92 ± 22.20	76.17 ± 20.29	58.36 ± 27.61
Physical role limitations**	76.15 ± 36.01	67.97 ± 38.90	48.36 ± 41.00
Pain	50.99 ± 23.94	62.53 ± 26.32	54.44 ± 27.16
General health**	73.28 ± 21.51	71.11 ± 18.38	57.50 ± 24.58
Vitality	62.80 ± 23.66	62.42 ± 23.45	53.84 ± 23.91
Social functioning	75.27 ± 25.22	75.78 ± 25.47	70.57 ± 29.58
Emotional role limitations*	75.39 ± 35.19	68.75 ± 39.93	52.59 ± 42.82
Mental health*	71.82 ± 22.12	68.06 ± 22.16	61.67 ± 24.27

Abbreviations – HC: healthy controls, HT: primary hypothyroidism, HP: hypoparathyroidism, W: women. Compared using one-way analysis of variance (Kruskal-Wallis). *p<0.001; **p<0.01.

Figure 1. Comparison of SF-36 scores between patients with hypoparathyroidism, hypothyroidism, and healthy controls.



HC: healthy controls; HT: hypothyroidism; HP: hypoparathyroidism; PF: physical functioning; PR: physical role limitations; GH: general health; VIT: vitality; SF: social functioning; ER: emotional role limitations; MH: mental health; SF-36: 36-item Medical Outcomes Short-Form Health Survey.

Table 4. Comorbidities emerging during conventional treatment in patients with chronic hypoparathyroidism.

	%
Hypertension	56.25
Type 2 diabetes mellitus	29.69
Chronic kidney disease – Stages 3 and 4*	13.15
Cardiovascular disease	1.56

Some patients developed more than one comorbidity. *Glomerular filtration rate < 60 mL/min.

Table 5. Correlation between clinical profile and quality of life in patients with hypoparathyroidism.

	PF	PR	Pain	GH	Vit	SF	ER	MH
Disease duration	-0.22	-0.18	-0.18	0.01	**-0.27***	-0.19	**-0.28***	-0.12
BMI	**-0.27***	-0.25	**0.26***	**-0.09***	-0.15	-0.02	-0.17	-0.21
Serum calcium	-0.21	**-0.27***	-0.17	-0.16	**-0.25***	-0.19	**-0.30***	-0.05
Ca x P product	-0.16	**-0.27***	-0.11	-0.05	-0.25	-0.14	**-0.27***	-0.06

Abbreviations – BMI: body mass index; PF: physical functioning; PR: physical role limitation; GH: general health; Vit: =vitality; SF: social functioning; ER: emotional role limitation; MH: mental health; Ca x P: calcium-phosphorus product, obtained by multiplying the serum calcium and phosphorus values. *p<0.05.

4 DISCUSSION

This study evaluated the profile, clinical evolution, and quality of life scores in patients with hypoparathyroidism receiving conventional therapy during follow-up at four public health centers and reference in endocrinology in Brazil.

The main etiology of HP was post-surgical, as identified in the present study, as well as by other authors[4, 12-14]. Our data also showed that patients with hypoparathyroidism were mostly women. Other studies in different countries have shown the same[1, 7]. We attribute this finding to the fact that thyroid diseases are more prevalent in women. The main cause for thyroidectomy observed in this and other studies was the treatment of multinodular thyroid disease[1, 15, 16].

The age of the patients in our study was similar to that reported by Arneiro et al.[17] in a study conducted in Curitiba (Paraná). While our patients had a mean age of 46 years at diagnosis and 56 years during treatment, the study from Curitiba reported the corresponding ages of 43 and 53 years, respectively. In Denmark, Underbjerg et al.[18] reported that their patients with HP had a median age of 49 years, which is also close to the mean age of our study patients.

In our study sample, 97% of the patients received calcium supplementation, while vitamin D supplementation was reported in 86% of the patients. Within these, 11% used only cholecalciferol, 34% used only calcitriol, and 41% used both. Also, 48% of the patients received thiazide diuretics. Astor et al.[19], reported that 18% of their patients with HP used no vitamin D

supplementation. In the literature, vitamin D supplementation can be absent in up to 30% of the patients with HP[7, 17]. Sikjaer et al.[20] reported that 62% of their patients with HP took supplemental calcium. Their patients also used exogenous vitamin D preparations of alfacalcidol (97%), ergocalciferol (5%), and colecalciferol (100%), and 13% used thiazides. Undebjerg et al.[7] found that 71% of their patients with HP used supplemental calcium and that the vitamin D preparation alfacalcidol was used by 70%, including 3% who used associated calcitriol. The use of thiazides was not mentioned in their study. The increased frequency of calcium supplementation in our study was due to the Brazilian diet being usually poor in calcium[21]. In Brazil, calcitriol is the only vitamin D preparation offered at no cost to patients with hypoparathyroidism, which explains the preference for this preparation by the physicians in the institutions included in this study.

The comorbidities observed in our study sample included, in increasing frequency of occurrence, cardiovascular diseases, cataract, nephrolithiasis, type 2 diabetes mellitus, and hypertension. Despite the comorbidities do occur over the years of conventional therapy, in patients with HP, their frequency varies and diverges in the series described in the literature. Underbjerg et al.[22] reported that 14.7% of the patients with HP presented cardiovascular disease and 1.9% had nephrolithiasis. Gafni et al.[13] observed that renal disease followed by cardiovascular disease were the most frequent complications in patients with HP.

Both the current literature and our study demonstrate that HP is a complex disease; therefore, bringing serum calcium levels back to normal is often not enough. Individuals with HP present physical (cramps, pain, fatigue, weakness), emotional (depression, anxiety), and neurocognitive ("brain fog") symptoms that can contribute to the low QoL observed in this population, even when treatment is apparently adequate[12-14].

Our data demonstrate that patients with combined HP+HT have lower quality of life scores in both physical and mental SF-36 domains compared with patients with HT alone and healthy controls. A pioneering study evaluating humor and well-being with an instrument other than the SF-36 observed humor disorders similar to anxiety among individuals with HP receiving conventional treatment[23]. Later studies using the SF-36 and other instruments agreed on the finding that conventional treatment is unable to restore quality of life scores[6, 10, 16, 24].

A systematic review of more than 372 studies[25] identified only five studies assessing quality of life in patients with hypoparathyroidism [19, 23, 26-28], all of which reported low QoL in this population. Other recent studies also demonstrate that hypoparathyroidism is a disease that negatively affects QoL[29-32]. Seven of the studies assessed QoL with the SF-36[19, 26-31]; the scores obtained were compared against the normative reference range in four of these studies[19, 27, 28,

[31] and against a control group in three of them[26, 29, 30]. When compared with normative data, Astor et al.[19], Cusano et al.[28] and Kontogeorgos et al[31] demonstrated that the presence of hypoparathyroidism affected all eight SF-36 domains.

Against a control group, we observed in our study that six out of the eight SF-36 domains were compromised in patients with HP+HT compared with healthy controls, the only spared domains being pain and social functioning. Sikjaer et al.[26] evaluated three different groups HP+HT versus HT versus "healthy controls" each one with 22 individuals and showed that compared to the healthy controls, patients with HP+HT had significantly decreased SF-36 scores in seven domains except the emotional role domain. Data from a Brazilian study using the Checklist-90-R (SCL-90-R) questionnaire corroborate the findings of low quality of life scores in patients with hypoparathyroidism compared with healthy controls[17].

Regarding correlations between the profile of the patients with hypoparathyroidism with each SF-36 domain, we identified that the disease duration correlated inversely with vitality and emotional role. Data about this correlation between disease duration and QoL in patients with HP are unavailable in the literature until now. We also compared the patients' age and quality of life and observed no correlation between both, corroborating findings reported in the literature[17, 19, 23].

The patients with HP+HT who completed the QoL questionnaire were asymptomatic and had normal serum calcium levels and calcium x phosphorus product. However, the lower the serum calcium level, the higher the quality scores regarding physical functioning, emotional role, and vitality. Arlt et al.[23] performed linear regression to analyze QoL measures from global severity index scores and found an inverse correlation between QoL scores and serum calcium levels, suggesting that maintaining higher serum calcium levels in HP can lead to a negative impact on QoL, a finding that was corroborated in our study. Other studies don't mention any about the correlation of QoL and serum calcium levels at these conditions we analyzed[25, 26]. Similarly, the lower the calcium x phosphorus product, the higher the QoL scores in the physical functioning and emotional role domains in patients with HP+HT. Although these correlations were all weak, our findings contrast with those by Astor et al.[19], who reported no correlation between serum calcium levels and QoL scores. This study by Astor et al. found a weak correlation between serum magnesium levels and physical functioning in patients with postsurgical hypoparathyroidism, which was also not confirmed in our study.

We observed that patients with increased body mass index (BMI) had lower quality of life scores in the domains of physical functioning, pain, and general health. We found no correlations in the literature between QoL and BMI in patients with HP until now.

Comparing the group of patients with combined HP+HT, versus those with HT alone. The presence of HP was associated with worse scores in the physical functioning, pain, vitality, and emotional role domains. Sikjaer et al.[26] observed differences in the physical functioning and physical role domains in HP+HT compared with those with HT alone. Jørgensen et al.[29] evaluated two HP+HT (n=14) versus HT (n=28) demonstrated significantly lower adjusted scores in the following QoL domains: physical functioning, role physical, bodily pain, general health, vitality, and mental health. Mazoni et al[30], testing QoL in a cohort of patients with differentiated thyroid cancer submitted to total thyroidectomy with (n = 89) and without (n = 89) chronic post-operative HP observed that compared to controls, patients with HP had significantly lower scores for physical functioning, general health, and emotional role limitations.

The association of $PTH^{1–84}$ with conventional treatment seems to reverse low quality of life scores in some domains in patients with HP[6, 33], although this finding is still controversial.

The use of a retrospective cohort and a cross-sectional analysis is a limitation of our study that hinders the evaluation of causal relationships. The SF-36 questionnaire has been used to evaluate QoL in many studies in patients with HP but is a generic instrument, therefore not specific to this population. Currently, no specific instrument is available to evaluate the emotional, cognitive, social, and physical aspects of patients with HP.

5 CONCLUSION

This study described the clinical profile and quality of life of patients with hypoparathyroidism receiving long-term conventional treatment. The conventional treatment allowed for optimal control of serum calcium levels and reversal of hyperphosphatemia with continuous use of multiple medication doses. Patients with hypoparathyroidism receiving conventional treatment developed several clinical complications over time, but we were unable to identify whether these complications were consequences of the hypoparathyroidism itself or due to therapies or specific comorbidities that are incident in this population. The conventional therapeutic approach in our study was unable to prevent low QoL scores in our patients with HP, and the maintenance of high serum calcium levels seemed with have lowered our patients' QoL. HP aggregated worse quality of life scores to HT. The findings of this study suggest that new strategies must be developed to improve QoL aspects related to hypoparathyroidism.

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