

REVIEW

Biochemical, bone and renal patterns in hyperparathyroidism associated with multiple endocrine neoplasia type 1

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Primary hyperparathyroidism associated with multiple endocrine neoplasia type 1 (hyperparathyroidism/multiple endocrine neoplasia type 1) differs in many aspects from sporadic hyperparathyroidism, which is the most frequently occurring form of hyperparathyroidism. Bone mineral density has frequently been studied in sporadic hyperparathyroidism but it has very rarely been examined in cases of hyperparathyroidism/multiple endocrine neoplasia type 1. Cortical bone mineral density in hyperparathyroidism/multiple endocrine neoplasia type 1 cases has only recently been examined, and early, severe and frequent bone mineral losses have been documented at this site. Early bone mineral losses are highly prevalent in the trabecular bone of patients with hyperparathyroidism/multiple endocrine neoplasia type 1. In summary, bone mineral disease in multiple endocrine neoplasia type 1-related hyperparathyroidism is an early, frequent and severe disturbance, occurring in both the cortical and trabecular bones. In addition, renal complications secondary to sporadic hyperparathyroidism are often studied, but very little work has been done on this issue in hyperparathyroidism/multiple endocrine neoplasia type 1. It has been recently verified that early, frequent, and severe renal lesions occur in patients with hyperparathyroidism/multiple endocrine neoplasia type 1, which may lead to increased morbidity and mortality. In this article we review the few available studies on bone mineral and renal disturbances in the setting of hyperparathyroidism/multiple endocrine neoplasia type 1. We performed a meta-analysis of the available data on bone mineral and renal disease in cases of multiple endocrine neoplasia type 1-related hyperparathyroidism.

KEYWORDS: Osteoporosis; Bone Demineralization; Nephrolithiasis; Outcome; Natural History.

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INTRODUCTION

Hyperparathyroidism in multiple endocrine neoplasia type 1

Primary hyperparathyroidism (HPT) is one of the most common endocrine diseases, with an estimated prevalence of 1–21 cases per 1,000 and an incidence of 27–30 cases per 100,000 person-years (1). HPT is biochemically characterized by hypercalcemia associated with abnormally high serum levels of parathyroid hormone (PTH). It is caused by parathyroid adenoma in 80–90% of cases, parathyroid hyperplasia in 10–15% of cases, and carcinoma in less than 1% of cases (2–4).

HPT occurs predominantly as a sporadic disease in 95% of cases; the remaining 5% of cases are hereditary forms of

the disease (2–6). It is worth noting that subtotal or total parathyroidectomy (PTx) is usually recommended for the treatment of inherited HPT cases, whereas adenomectomy is indicated for the vast majority of sporadic HPT cases (6–8). As part of the familial HPT subset, HPT associated with multiple endocrine neoplasia type 1 (HPT/MEN1) comprises up to 4.5% of all HPT cases (9). MEN1 is a complex autosomal-dominant hereditary disorder characterized by a high predisposition to develop a wide spectrum of endocrine and non-endocrine tumors. MEN1 is defined by the presence of tumors in at least two of the three main endocrine glands involved in this syndrome (i.e., the parathyroids, the pituitary gland, and the endocrine cells of the pancreas/duodenum). Familial MEN1 is determined by the identification of at least one of the major tumors in a family member of the index case with MEN1 (5). HPT is the most frequent tumor in MEN1, reaching nearly complete penetrance by the time the patient is 50 years of age. Sporadic HPT (S-HPT) differs from MEN1-related HPT in many ways and the recognition of these differences may help to reveal the diagnosis of MEN1 (Table 1) (10).

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No potential conflict of interest was reported.

Table 1 - Classic comparisons of sporadic HPT and MEN1-related HPT.

Clinical characteristic	MEN1-related HPT	Sporadic HPT
Onset	Earlier (20–30 years)	Later (50–70 years)
Sex (M:F)	1:1	1:3
Germline <i>MEN1</i> mutation	Yes	No
Pathology	Multiglandular (hyperplasia)	Uniglandular (adenoma)
Surgery	Total or subtotal PTx	Adenomectomy
Timectomy	Yes	No
Other associated tumors	Yes	No
Adverse effects of hypergastrinemia	Yes	No
Cure rate	Low	High (> 90%)
HPT recurrence rate after PTx	High (~50%)	Rare

HPT: primary hyperparathyroidism. MEN1: multiple endocrine neoplasia type 1. PTx: parathyroidectomy.

A marked change in the clinical picture of HPT occurred after the widespread introduction of annual calcium measurements using multichannel analyzers in the mid 1970s in the USA and Europe. Beyond increasing prevalence of S-HPT, this practice resulted in crescent diagnosis of the asymptomatic form of HPT and progressive decreasing of symptomatic cases. Thus, renal, bone and neurological complications secondary to S-HPT are increasingly uncommon nowadays in countries where routine measurements of serum calcium are performed (1–4).

At present, most S-HPT cases are asymptomatic and characterized by vague neurocognitive symptoms such as pain, fatigue, depression, and milder degrees of bone and renal disease mainly characterized for reduced creatinine clearance rate and bone demineralization (1–4).

Other tumors associated with MEN1

Multiple duodenal gastrinomas and non-functioning pancreatic neuroendocrine tumors occur in 40% and 34% of cases, respectively, at around 50 years of age. Because of their high potential for malignancy, these types of tumors are the major causes of MEN1-related morbidity and mortality (5,11,12). Several tumors that may be associated with MEN1 have a high potency for malignancy but occur at low frequencies (2%), such as glucagonomas, somatostatinomas and pancreatic polypeptide or vasoactive intestinal polypeptide secreting tumors. (5).

Pituitary tumors may occur in up to 30–40% of the patients with MEN1, mostly in the form of prolactinomas and non-functioning and co-secreting pituitary adenomas. In addition, corticotrophin-secreting tumors may potentially lead to Cushing’s disease. It should also be noted that acromegaly/gigantism is less prevalent in MEN1, and other forms of familial acromegaly should be ruled out (13–19).

A wide spectrum of other endocrine tumors may be present, such as thymic, bronchial and gastric carcinoids and non-functioning adrenocortical tumors, as well as non-endocrine tumors, such as facial angiofibromas, collagenomas, lipomas, meningiomas, and pinealomas (5,20,21).

Genetic aspects

The gene responsible for MEN1 syndrome, *MEN1* gene, is localized to chromosome 11q13 and belongs to a class of tumor suppressor genes. The *MEN1* gene codes Menin, a ubiquitously expressed nuclear protein that interacts directly with proteins involved in transcriptional regulation, genome stability, cell division, and cell cycle control (20). More than 1,000 mutations of the *MEN1* gene associated with MEN1 syndrome have been described to

date (22). Also, in case series, new germline *MEN1* mutations were documented by our group and all types of mutations have been observed, mostly those leading to the truncation of the Menin protein (23,24). Point mutations in the *MEN1* gene represent up to 20% of cases, as recently confirmed by us (www.arup.utah.edu/database/men1/classification.php). Furthermore, Menin interacts with several partners (25–28).

OBJECTIVE

Very few papers have addressed the bone mineral and renal complications that occur secondary to MEN1-related HPT, the shift to the asymptomatic form, and the natural history of this disorder. In this review, we present a meta-analysis of the current literature on this subject.

Biochemical, bone mineral and renal disease in HPT related to MEN1

Burgess series. The first study on bone mineral status in MEN1 was published by Burgess et al. in 1998 (29). In this paper, 29 women with HPT from a large Tasmanian family with MEN1 were studied. Bone mineral density (BMD) was measured at only two main bone sites: the femoral neck (FN) and the lumbar spine (LS). A high frequency of osteoporosis (T-score <-2.5) was verified in the FN (44.8%) and LS (25.6%), whereas osteopenia (T-score <-1.0 and >-2.5) was also prevalent in the FN (41.4%) and LS (34.5%). Considering all cases with reduced BMD (T-score <-1.0), the FN was more compromised (86.2%) than the LS (60.1%). Of note, normal BMD in the LS was found in 37.9% of cases whereas normal BMD in the FN was found in 13.8% of cases, suggesting a preferential demineralization in mixed bone rather than in trabecular bone. The high prevalence of osteopenia and osteoporosis in the LS of these cases might suggest that in HPT/MEN1 patients the trabecular bone is less metabolically “protected” than in asymptomatic S-HPT patients (29–31). The finding of severe osteopenia at the FN by 35 years of age (T-score <-2.0) in four of the nine cases (44%) of the MEN1 subset with uncontrolled HPT suggest an early bone disease in this MEN1-related HPT subset (29). One of the illustrations in this study showed that there were 20 women who were younger than 50 years. Half of them (10/20; 50%) had T-scores <-2.0 for the FN and seven of them had such scores for the LS (35%). The individual Z-scores of the studied cases were not published, preventing an analysis of the Z-scores for cases younger than 50 years, as is presently recommended. Also, reduced BMD is

considered when the Z-score is <-2.0 in individuals younger than 50 years (32,33).

Although there were unknown numbers of untreated and treated patients, BMD in the subset of patients with controlled HPT was better than that in patients with uncontrolled HPT (as measured by the Z-score), indicating that previous BMD reports could be even more compromised initially suspected. In addition, five patients could be analyzed before and after successful subtotal parathyroidectomy in this study. Although the number of patients was limited, a marked increase in bone mass was noted at the LS and FN over a mean follow-up period of 18 months, suggesting a possible beneficial effect of early surgical treatment for treating HPT/MEN1 cases, similar to that observed in S-HPT cases (29,34,35).

Our first case series. The second paper addressing this topic was published in 2008 and describes a large Brazilian family with MEN1 and 50 clinically and/or genetically affected members over six generations (36). BMD analysis was performed in 20 HPT/MEN1 patients: 17 untreated cases and three cases with uncontrolled HPT due to previously unsuccessful parathyroid surgeries. In the 20 affected family members, we examined cortical bone BMD in HPT/MEN1 for the firstly approach (36).

Although the number of patients studied was limited, it was possible to analyze data from both men and women and a preliminary natural history of bone disease in MEN1 could be developed. Of the 20 cases, 75% and 60% of them had osteoporosis ($T <-2.5$) and osteopenia ($T <-1.0$ and >-2.5), respectively, in at least one of the three main bone sites. Considering all cases with reduced BMD ($T <-1.0$), the most compromised bone site was the proximal one-third of the distal radius (90%; 1/3DR), followed by the FN (65%), and LS (60%) (36).

Osteoporosis was predominant in 1/3DR (55%), followed by the LS (40%), and FN (20%). The degree of bone demineralization was more severe in the cortical bone ($T = -2.87 \pm 0.32$ for the 1/3DR), although L1-L4 ($T = -1.92 \pm 0.39$) and the FN ($T = -1.48 \pm 0.27$) were also affected. Moreover, cortical bone was the most compromised bone site in these MEN1-related HPT cases, as it was the first to be affected and presented with the highest prevalence of bone demineralization and the worst BMD values (36). These findings are quite similar to those that have been reported for S-HPT (30,31,35).

Data from our study (36) reinforce the findings of Burgess et al. (29) by reporting a high frequency of reduced BMD of the LS in the subset of MEN1-related HPT cases. In both studies, patients presented with serum PTH levels that were 2- to 3-fold higher than the upper limit of the normal range, as is frequently observed in asymptomatic S-HPT (34,35). However, the relative protection of vertebral bone sites, secondary to the anabolic effect of these PTH values on trabecular bone, was not observed in the HPT/MEN1 subset, in contrast with data on S-HPT (29,31,36,37).

Norton case series. In a study on the long-term outcome of PTx in 84 consecutive MEN1 cases with HPT associated with gastrinoma (HPT/gastrinoma), Norton et al. (38) reported a more severe form of HPT. In these cases, the disease was characterized by a higher frequency of nephrolithiasis at the time of diagnosis (62% vs. $40 \pm 6\%$ from seven literature series), a higher frequency of recurrent HPT (44% vs. 17% from 15 literature series, subtotal PTx), and higher levels of PTH (2.4-fold vs. 1.67 ± 0.38 from eight literature series). In addition, BMD studies were performed

in 56 of the 84 patients and bone demineralization was observed in 47% of them (Z-scores were <-2.0 in at least one of the analyzed bone sites). These data led the authors to suggest that a more virulent form of HPT presents in MEN1 cases with HPT/gastrinoma. However, the authors did not indicate which bone sites had been examined (38). Of note, Burgess et al. found no association between reduced bone mass and a restricted number of cases with gastrinoma (29), whereas no data on the BMD status of the subset of cases of HPT/gastrinoma were available in our first case series (36).

Eller-Vainicher case series. This study was the first to compare BMD data from a MEN1-related HPT series with BMD data from S-HPT cases (39). Findings from 469 S-HPT cases were compared with those of 64 HPT/MEN1 patients (36 index cases and 28 affected relatives).

There was no significant difference between HPT/MEN1 index cases and their affected family members in terms of clinical, biochemical, and BMD findings. However, HPT/MEN1 patients had a tendency to be younger and have lower serum levels of phosphate and PTH than patients with S-HPT. Both HPT occurring before 50 years of age and inappropriately normal PTH values were considered independent, predisposing factors to MEN1-related HPT. Also, the likelihood of association with the MEN1 syndrome was 13.5-fold greater when both factors were present (39).

A BMD analysis of LS and FN bone sites was conducted in 432 patients (388 S-HPT and 44 HPT/MEN1 cases). In both sites, bone mineral losses were more compromised in the HPT/MEN1 subset than in the S-HPT subset (Z-scores: LS, -1.33 ± 1.23 vs. -0.74 ± 1.40 ; FN, -1.13 ± 0.96 vs. -0.60 ± 1.07). The prevalence of nephrolithiasis was similarly high in both groups (57.8% vs. 55.2%) (39).

It was concluded that bone mineral disease is more severe in cases with MEN1-related HPT than in cases with S-HPT. These findings are in agreement with previous evidence indicating the lack of relative protection of the vertebral (trabecular) bone in HPT/MEN1 (10,29,36).

Kann case series. Recently, Kann et al. (40) studied BMD in 23 patients with MEN1-related HPT using peripheral quantitative computed tomography, and they confirmed the previous findings of marked bone demineralization in HPT/MEN1. Despite the limited number of patients and the absence of statistical significance, it was suggested that several other pathological conditions that potentially occur in MEN1 could be responsible, in part, for the bone demineralization observed in these cases. The conditions cited as potentially influencers of the BMD values were gonadotrophic and somatotrophic insufficiency, hypercortisolism and a history of upper gastrointestinal surgery (40).

BMD after parathyroidectomy in HPT associated with MEN1

The fifth study that examined BMD status in MEN1-related HPT described short-term BMD changes that occurred after PTx in 16 HPT/MEN1 cases. A significant recovery in terms of BMD at the LS and FN, but not in the 1/3DR, was documented in 16 HPT/MEN1 patients at 15 months after PTx (41). These data contrast with the findings of BMD recovery that were verified in cases with S-HPT, in which a BMD gain was noticed in all three bone sites (35). Several factors potentially influence or even determine the differences in the patterns of BMD recovery in HPT/MEN1 compared with S-HPT: different surgical protocols (total PTx in HPT/MEN1 vs. adenomectomy in S-HPT), the

amount of remnant parathyroid tissue, the degree of success of parathyroid auto-implantations, and the lack of proper PTH action for long periods in patients who undergo total PTx. Most cases reached appropriate PTH levels, as produced by the parathyroid implant, only 9 months after surgery (41).

Further long-term studies are needed to elucidate whether a cortical bone BMD recovery after PTx would occur in HPT/MEN1 cases. As the metabolic activity of cortical bone is slower than that of trabecular bone (41), it would be expected that a long-term BMD recovery at the 1/3DR may occur in HPT/MEN1 patients under more prolonged PTH action. Furthermore, we had the opportunity to first report the basal and post-PTx values of bone formation and reabsorption markers osteocalcin and CTX, respectively, in HPT/MEN1 (41). The levels of basal bone markers varied from mildly high to normal, and a significant decrease was observed in these cases after total PTx followed by parathyroid auto-implantation in the non-dominant forearm (41).

Our second case series

Recently, we reported the first study to examine the early and late outcomes of bone mineral and renal complications in 36 patients with uncontrolled HPT from eight MEN1 families (10). These topics have been extensively studied in sets of cases with S-HPT (30,34,35,42).

The peculiar clinical characteristics of these patients provided the conditions required to study the outcome of HPT cases associated with MEN1 (Table 2). Bone demineralization was early, extensive, severe, and progressive in these cases. The 1/3DR (cortical bone) was the preferentially compromised bone site in younger patients and asymptomatic cases (10).

In addition, the high prevalence of nephrolithiasis in cases younger than 30 years and in most cases older than this age suggested that a relatively short period of asymptomatic HPT may be the rule for MEN1, in contrast to S-HPT cases (Table 2) (10,35). However, as only 15 HPT/MEN1 cases younger than 30 years and nine asymptomatic HPT/MEN1 cases were available to be studied (10,35), further longitudinal BMD data are needed in this set of cases.

In this study, progressive bone mineral loss could be observed with aging and long-standing HPT disease. Thus, in the older group (>50 years) bone demineralization was significantly more frequent, extensive, and severe. Furthermore, the older group had higher frequencies of previous fractures and a progressive decrease in renal function associated with a high frequency of nephrolithiasis-related co-morbidities (10) (Table 2).

Progressive demineralization of the cortical and trabecular bones was associated with the duration of HPT disease; specifically, in cortical bone, this progression was also observed in patients who had had HPT disease for more than 10–20 years (Table 2). This bone demineralization pattern differs from that reported for S-HPT, in which stable bone disease occurred at these sites for the first 10 years of disease followed by progressive demineralization of cortical bone for up to 15 years (10,35).

DISCUSSION

We performed a meta-analysis of data on bone mineral status and renal complications secondary to HPT associated with MEN1.

Bone disease

Seven investigations have addressed this subject to date. BMD in HPT/MEN1 cases was examined by most of these studies, although different bone sites were analyzed and different parameters were applied limiting an integrated analysis (Table 3).

The LS, a site rich in trabecular bone, and the FN, a site composed of mixed amounts of trabecular and cortical bone, were analyzed in five of the seven studies by bone densitometry (10,29,36,39,41). The 1/3DR, consisting mainly of cortical bone, is the preferentially compromised bone site in S-HPT (30,34,35,42); however, this site was examined in only three of the latter five studies (10,36,41). One study did not mention which bone sites were analyzed (38). A recent study used peripheral quantitative computed tomography instead of dual-energy X-ray absorptiometry to analyze the bone mineral status (40) (Table 3).

Of note, different parameters were used to analyze BMD in these studies. T-score values were preferentially used in some studies, while Z-score values were utilized in others, depending on the objectives and criteria recommended at each time (Table 3) (29,41). At present, the criteria applied for analyzing BMD were defined and officially adopted by the International Society for Clinical Densitometry (ISCD) in 2008 and accepted by consensus on HPT in 2009 (32,33). According to these criteria, BMD values should be measured by dual-energy X-ray absorptiometry at four major bone sites: the lumbar spine (L1-L4), the FN, total hip (TH), and the 1/3DR (32,33). The Z-score should be used for patients younger than 50 years, whereas the T-score should be used for patients older than 50 years. Z-score values < -2.0 or T-score values < -1.0 indicate a reduced BMD, T-score values between -1.0 and -2.5 indicate osteopenia and T-scores < -2.5 indicate osteoporosis (32,33). These new criteria have been used in one BMD study of HPT/MEN1 cases so far (10).

The lack of available individual BMD data and the superposition of patients who had been studied in an earlier case sets were noticed in some of these studies, limiting the possibility of a combined BMD analysis using the ISCD criteria (32,33). A combination analysis using the present ISCD criteria, excluding interposition of patients from different studies, could be applied, in part, by using BMD data from two studies (Table 4) (10,29).

ISCD criteria were applied to the findings obtained from patients older than 50 years from the two latter studies; BMD data from the LS and FN were reanalyzed for 24 patients and data from the TH and 1/3DR were reanalyzed for 14 cases. BMD (T-score < -1.0) was found to be reduced in 79.1%, 83.3%, 100%, and 92.9% of cases at the LS, FN, TH, and 1/3DR sites, respectively. Osteoporosis was more prevalent than osteopenia in the LS (58.3% vs. 20.8%) and in the 1/3DR (57.1% vs. 35.7%), but this condition was equally prevalent in the FN (41.6%) and osteopenia was dominant in TH (78.6% vs. 21.4%) (10,29). In this evaluation, we included the older cases reported by Burgess et al., despite the presence of patients with uncontrolled (4/9 cases) and controlled HPT (5/9 cases). These findings confirm recent data on outcomes in MEN1-related HPT that indicate an increased frequency of age-related bone demineralization in all bone sites in 15 untreated HPT/MEN1 cases (Table 4) (10).

Presently, it is preferable that BMD data obtained from younger patients be analyzed using the ISCD criteria. To

Table 2 - Early and late outcomes of renal and bone disease in MEN1-related HPT.

Characteristics of 36 MEN1-related HPT cases	
<ul style="list-style-type: none"> ● Symptomatic cases, predominantly (75%) ● Untreated cases, mainly (86.1%) ● All uncontrolled HPT ● Long-term disease (15.4 ± 12.8 years) (61%) ● Presence of young and old cases, including nine asymptomatic cases (25%) 	
Specific bone mineral profile (distinguishing characteristic from the profile of sporadic HPT)	
Severe demineralization of cortical (1/3DR) and trabecular bone (LS)	
Bone mineral outcome	
Early stages	Late stages
<ul style="list-style-type: none"> ● Preferential demineralization in 1/3DR, which may be the only compromised bone site ● Absence of vertebral bone protection ● Lower number of compromised bone sites in asymptomatic cases and symptomatic cases with a shorter estimated period of disease (less than 10 years) ● Bone disease may precede renal disease 	<ul style="list-style-type: none"> ● All bone sites are frequently demineralized and more severely compromised ● Vertebral and cortical bone are equally compromised, with a predominance of osteoporosis ● Higher number of compromised bone sites in symptomatic cases with longer estimated period of disease (after 10 or 20 years) ● Higher frequency of fracture in cases older than 50 years old (40% vs. 4.8%)
Proximal one-third of the distal radius	
Lower BMD in:	
<ul style="list-style-type: none"> ● cases with a history of HPT for more than 10 years and more than 20 years ● patients with HPT/gastrinoma ● patients with higher levels of calcium 	
Lumbar spine	
Lower BMD in:	
<ul style="list-style-type: none"> ● patients who have had HPT for a longer time 	
Renal disease outcome	
<ul style="list-style-type: none"> ● Early onset of urolithiasis (86.2%, <30 years) ● High frequency of therapeutic procedures to urolithiasis as surgery and lithotripsy (47.2%) ● Higher prevalence of different degrees of renal insufficiency in cases older than 50 years old (40%) 	

Data were obtained from Lourenço et al. (10). MEN1: multiple endocrine neoplasia type 1. HPT: primary hyperparathyroidism. LS: lumbar spine. 1/3DR: proximal one-third of the distal radius. BMD: bone mineral density.

date, these criteria have been applied only to one HPT/MEN1 case series (10). An early onset of reduced BMD was found in half (6/12) of patients below the age of 30 years. Furthermore, in this study, 40% of patients younger than 50 years had reduced BMD at the 1/3DR compared with 23.8%, 25%, and 22.2% at the LS, FN, and TH, respectively. Reduced BMD (Z-score <-2.0) in at least one bone site was noticed in 62% of all patients younger than 50 years (12/21), confirming the presence of early bone demineralization

in MEN1-related HPT. In addition, this study confirms previous BMD data obtained using T-score values and indicates that bone demineralization in MEN1-related HPT is most likely an early event (Table 4) (10,29). However, further BMD data obtained from younger HPT/MEN1 cases are necessary to clarify this issue.

In the subset of patients with S-HPT, the asymptomatic form is more prevalent in developed countries. The classical bone demineralization pattern of this condition

Table 3 - The methods used in the seven studies that examined bone mineral status in MEN1-related HPT.

Literature/Method	Number of patients	Bone sites	Criteria used in BMD analysis
Burgess et al. (29)/DXA	29	LS FN	T-scores*: Osteopenia, <-1.0 Severe osteopenia, <-2.0 Osteoporosis, <-2.5 Z-score*: >-1.0; <-1.0; <-2.0
Lourenço et al. (36)/DXA	20	LS FN 1/3 DR	T-scores*: Osteopenia, <-1.0 Osteoporosis, <-2.5
Norton et al. (38)	56	Not available	Any Z score ≤-2.0
Eller-Vainicher et al. (39)/DXA	44	LS FN	Z score ≤-2.0
Coutinho et al. (41)/DXA	16	LS FN TH 1/3 DR UDR	Mean values of: g/cm ² , T- and Z-scores before/after PTx
Lourenço et al. (10)/DXA	36	LS FN TH 1/3 DR	T-scores**: Reduced BMD, <-1.0 Osteopenia, -1.0 to -2.5 Osteoporosis, <-2.5 Z score***: Reduced BMD, ≤-2.0
Khan et al. (40)/pqCT (g/cm ³)	23	Forearm Trabecular BMD/ total BMD	Z-score: >-1: normal -1 to -2: low <-2: reduced

BMD: bone mineral density. MEN1: multiple endocrine neoplasia type 1. HPT: primary hyperparathyroidism. DXA: dual-energy X-ray absorptiometry. pqCT: peripheral quantitative computed tomography. LS: lumbar spine. FN: femoral neck. 1/3DR: proximal one-third of the distal radius. TH: total hip. UDR: ultra distal radius. T-scores: difference from the mean BMD value in a healthy young reference population, in SD units. Z-scores: age-matched comparison, in SD units. *: independent of age. PTx: parathyroidectomy. **: performed in patients older than 50 years of age. ***: performed in patients younger than 50 years of age.

is characterized by the early and preferential loss of cortical bone (1-4,30,31,35). It was speculated that long-term asymptomatic hypercalcemia could occur in HPT/MEN1 cases, similar to that reported in S-HPT (43). However, as far as we know, no prospective study on this specific topic has been performed to date. In this context, the BMD status of asymptomatic HPT/MEN1 cases has been rarely studied (10). So far, only nine asymptomatic HPT/MEN1 cases have been analyzed in a cross-sectional study, although early bone losses were documented in 44.4% of the cases with a predominance of cortical bone demineralization. Interestingly, eight of these patients (88.9%) were younger than 30 years.

Renal disease in HPT associated with MEN1

A high frequency of early-onset nephrolithiasis was documented in our patients before 30 years of age (86.2%), suggesting the existence of a relatively short period of asymptomatic hypercalcemia in this condition. Occasionally, two asymptomatic cases became symptomatic soon after the diagnosis of HPT (10). These findings supported the hypothesis that patients with MEN1-related HPT have a higher susceptibility to nephrolithiasis than S-HPT patients (10,39,44,45).

Consistent with this view, Christopoulos et al. (45) reported a high frequency of renal calculi in HPT/MEN1 patients before 30 years of age: 15 of the 17 younger patients (82%) in the report presented with nephrolithiasis. Of note, only three of our nine HPT/MEN1 patients with no renal calculi were older than 30 years, reinforcing the early onset

of nephrolithiasis in MEN1-related HPT (10). These two studies revealed a high frequency of kidney co-morbidities secondary to nephrolithiasis (10,45). Taken together, these two studies analyzed a total of 62 patients and 46 of them (74.2%) had renal calculi. In 26 of these 46 cases (56.5%), sessions of extra-corporeal shock-wave lithotripsy and/or surgical procedures were needed to treat nephrolithiasis. Three cases (6.5%) required unilateral nephrectomy because of pyonephrosis and staghorn calculus presented as the first renal clinical manifestation, acute obstructive urolithiasis resulting in renal abscess and sepsis after only a few crisis of renal calculi and chronic urolithiasis associated with recurrent renal infections leading to complete loss of kidney function, respectively (10,45). Different degrees of renal insufficiency were reported in seven of 29 HPT/MEN1 cases (19.4%). In two patients older than 47 years of age, creatinine clearance rates less than 44 ml/min/1.73 m² were reported (10).

HPT associated with MEN1 and gastrinoma

Norton et al. (38) reviewed seven series of MEN1-related HPT and the frequency of nephrolithiasis in this group was 40 ± 6%. It was suggested that MEN1 patients with HPT/gastrinoma had a higher susceptibility to the development of nephrolithiasis (62%) and a higher frequency of reduced BMD (46%). However, other studies revealed similar frequencies for nephrolithiasis (57.8–75%), independent of the presence of gastrinoma (10,39,45). In one of these series, a higher frequency of nephrolithiasis, although not statistically significant, was found in MEN1-related HPT cases with gastrinoma than in MEN1-related HPT cases without

Table 4 - Comparative analysis of BMD findings using the ISCD (2009) criteria (32,33).

BMD pattern in MEN1-related HPT	LS (n)	FN (n)	TH (n)	1/3DR (n)
Group younger than 50 years of age with reduced BMD (Z < -2.0)				
Burgess et al. (29)	-	-	-	-
Lourenço et al. (10)	23.8 (5/21)	25 (5/20)	22.2 (4/18)	40 (8/20)
Total	23.8 (5/21)	25 (5/20)	22.2 (4/18)	40 (8/20)
Group older than 50 years of age with reduced BMD (T < -1.0)				
Burgess et al. (29)	77.7 (7/9)	100 (9/9)	-	-
Lourenço et al. (10)	80 (12/15)	73.3 (11/15)	100 (14/14)	92.9 (13/14)
Total	79.1 (19/24)	83.3 (20/24)	100 (14/14)	92.9 (13/14)
Group older than 50 years of age with osteoporosis (T < -2.5)				
Burgess et al. (29)	44.4 (4/9)	66.6 (6/9)	-	-
Lourenço et al. (10)	67.7 (10/15)	26.7 (4/15)	21.4 (3/14)	57.1 (8/14)
Total	58.3 (14/24)	41.6 (10/24)	21.4 (3/14)	57.1 (8/14)
Group older than 50 years of age with osteopenia (-2.5 < T < -1.0)				
Burgess et al. (29)	33.3 (3/9)	33.3 (3/9)	-	-
Lourenço et al. (10)	13.3 (2/15)	46.7 (7/15)	78.6 (11/14)	35.7 (5/14)
Total	20.8 (5/24)	41.6 (10/24)	78.6 (11/14)	35.7 (5/14)
Reduced BMD: Z < -2.0 in younger patients (<50 years) and T < -1 in older patients (>50 years)				
Burgess et al. (29)	77.7 (7/9)*	100 (9/9)*	-	-
Lourenço et al. (10)	47.2 (17/36)	45.7 (16/35)	56.2 (18/32)	61.8 (21/34)
Total	53.3 (24/45)	56.8 (25/44)	56.3 (18/32)	61.8 (21/34)
Reduced BMD (Z < -2.0), independent of age				
Burgess et al. (29)	20.7 (6/29)	27.6 (8/29)	-	-
Lourenço et al. (10)	36.1 (13/36)	20 (7/35)	18.8 (6/32)	47.1 (16/34)
Total	29.2 (19/65)	23.4 (15/64)	18.8 (6/32)	47.1 (16/34)

BMD: bone mineral density. ISCD: International Society for Clinical Densitometry. MEN1: multiple endocrine neoplasia type 1. HPT: primary hyperparathyroidism. LS: lumbar spine. FN: femoral neck. TH: total hip. 1/3DR: proximal one-third of the distal radius. T-scores: difference from the mean BMD value in a healthy young reference population, in SD units. Z-scores: age-matched comparison, in SD units. *: only patients older than 50 years were included.

gastrinoma (93.3% vs. 71.4%) (10). Bias might have occurred with these data because of the limited number of patients available for comparisons. Of note, the onset of gastrinomas in patients with MEN1 usually occurs between 30–50 years of age, when most patients have already developed renal calculi (10,45).

In the same study, using ISCD criteria, MEN1 cases with HPT/ gastrinoma had higher frequencies of reduced BMD independent of the bone site than HPT/MEN1 cases without gastrinoma (86.7% vs. 52.4%, $p < 0.03$) (10). Demineralization at the 1/3DR in HPT/gastrinoma cases was significantly more severe than in HPT-only MEN1 cases ($p < 0.013$) (10). In addition, there was a tendency for higher PTH and calcium levels in our HPT/gastrinoma cases, reinforcing data reported by Norton et al. (10,38). When individual data from our second case series were reviewed and the criteria used by Norton et al. were applied ($Z < -2.0$, independent of the bone site), 66.7% of the cases presented reduced BMD independent of the presence of gastrinoma. However, no appropriate comparisons could be performed between these two studies, as BMD data for the specific bone sites were not available for the cases reported by Norton et al. (38) and because we had a limited number of gastrinoma/MEN1 cases (10).

Biochemical data on HPT associated with MEN1

Several studies have reported mild biochemical disease associated with MEN1-related HPT, with modestly elevated

levels of calcium and a predominance of PTH values that are 2- to 3-fold above the upper limit of the normal range. Two earlier studies demonstrated a direct correlation between age and calcium/PTH values in a subset of patients with MEN1-related HPT, which is probably associated with the progressive development of parathyroid hyperplasia and the asynchronous onset of HPT disease in the different parathyroid glands (46,47). A tendency toward increasing PTH levels was also observed in older patients after long periods of HPT disease (10).

Furthermore, Eller-Vainicher et al. (39) reported a direct association between increasing PTH/calcium levels and aging. These authors also reported an association between inappropriately normal serum PTH values and age below 50 years with presence of HPT/MEN1. Thus, fifteen of the 40 HPT/MEN1 patients younger than 50 years (37.5%) had inappropriately normal PTH levels. Additionally, cases younger than 50 years and presenting inappropriately normal PTH levels had 13.5 fold higher likelihood of association with MEN1 syndrome than patients with 50 years old or more and presenting high serum levels of PTH. (39).

Combining data from Burgess et al. 's study and our own, the prevalence of inappropriately normal PTH levels was 9.2% (6/65), independent of age (10,29). However, the real prevalence could be even higher once controlled and uncontrolled HPT cases from the study by Burgess et al. (29) are included in the present evaluation. One of the six

cases in our series had asymptomatic HPT and another had recurrent HPT (10). It is possible that HPT/MEN1 cases in these two studies (10,29) were diagnosed later than in the study by Eller-Vainicher et al. (39). In addition, the laboratory diagnosis of HPT in the Eller-Vainicher study may have been more rigorously performed, as serum PTH levels were considered after adjusting for age and sex (39).

Biochemical data and BMD

Correlations between biochemical and BMD data in HPT/MEN1 are contrasting. Burgess et al. reported an inverse correlation between PTH levels and LS and FN BMD findings, but not with regard to calcium levels. Conversely, no correlation between PTH levels with BMD values were observed in other studies (10,39). Of note, an inverse correlation between calcium levels and 1/3 DR BMD values was reported (10).

Other conditions associated with MEN1 and BMD

Recently, Kaan et al. (40) used peripheral quantitative computed tomography to analyze BMD and reported a higher prevalence of bone demineralization in HPT/MEN1 cases (48% in trabecular BMD and 60% in total BMD) than in the normal population (15%). However, most of these cases had been previously submitted to PTx and, thus, a postsurgical BMD gain had probably occurred. Thus, the real prevalence of bone demineralization in this group of patients could be even higher. Despite the limited number of cases and the lack of statistical significance of the findings, it was suggested that other associated factors might influence the BMD status of these cases (40). This conclusion was based on the presence of five cases (22.7%) with hypopituitarism secondary to gonadotrophic and/or somatotrophic insufficiency, three cases with hypercortisolism (13.6%), and 12 cases (52%) with previous surgeries to the upper gastrointestinal tract (40). Other studies that examined this subject produced different results. Burgess et al. (29) found no association between hypogonadism secondary to prolactinoma or menopausal status and reduced BMD. Eller-Vainicher reported 10 cases with hyperprolactinemia but without hypogonadism and no cases with hypopituitarism (39). Also, we recently reported no difference in BMD status between six postmenopausal and 12 premenopausal women, as well as between 10 cases with and 26 cases without prolactinoma (10). In this latter study, the HPT/MEN1 cases with prolactinoma had been successfully treated with bromocriptine or a similar agent and a potential BMD recovery might have interfered with the statistical results. It is most likely that prolactinoma and menopause occur much more frequently in MEN1 than hypopituitarism secondary to pituitary macroadenoma or hypercortisolism, in contrast with data from Kaan et al. (40). However, large studies are needed to clarify this issue.

The prevalence of pituitary adenoma in familial MEN1 was evaluated by Verges et al. and found to be 34% (14). Prolactinoma was the most frequent pituitary tumor (68%), and macroadenoma was highly prevalent in this sample (85%) (14). Based on these data, we could estimate that one-fifth and one-third of MEN1 patients, respectively, might potentially develop prolactinomas and macroadenomas. However, the actual prevalence of hypopituitarism in MEN1 is currently unknown. Somatotropinomas are relatively rare in MEN1

(14,15) and should be differentiated from familial and isolated acromegaly/gigantism caused by other gene mutations, such as *AIP* (13,16-19). Hypercortisolism occurs infrequently in MEN1 (up to 7% of cases) (14), although several studies involving large series reported no case with hypercortisolism in MEN1 (10,36,39,41).

Of note, Kaan et al. analyzed the potential impact of previous gastrointestinal surgeries on BMD and found no significant correlations (40). Although several factors may potentially worsen bone mineral status in MEN1, a satisfactory BMD recovery could be provided to patients if MEN1-related conditions are promptly diagnosed and treated.

Genetics and MEN1

BMD studies on HPT/MEN1 have also examined connections with the genetic status of these cases. Burgess et al. studied 29 affected women from a large MEN1 family harboring a known germline *MEN1* mutation (29). However, genotyping could not be performed on all of the studied cases. Thus, the possibility of phenocopies, which may occur in up to 5% of MEN1 families (20,48), could not be fully excluded from these cases.

Eller-Vainicher studied a series of 64 affected patients from 36 unrelated MEN1 families (39). A germline *MEN1* mutation was found in 31 index cases but not in the remaining three index cases that were included in this sample of familial MEN1 genealogies because they had typical MEN1-affected relatives.

In three other studies, all affected cases belonging to MEN1 families harboring novel or previously reported germline *MEN1* mutations and all index cases, as well as affected family members, were genetically documented (10,23,24,36,41).

Norton et al. reported a familial history of MEN1 in 68 of the 81 (81%) studied cases (38). A germline *MEN1* mutation was found in 61 cases (75.3%), nine cases had no *MEN1* mutation and the genetic status of 14 other cases was unknown. Kaan found a germline *MEN1* mutation in all of the cases studied, except one (22/23; 95.7%) (40).

It is worth noting that an appropriate selection of genetically characterized MEN1 cases is needed, as the pathogenesis of sporadic MEN1 and of familial MEN1 cases that do not harbor a germline *MEN1* mutation are different.

Prospective studies

Despite the absence of prospective studies focusing on the early and late outcomes of renal and bone mineral complications in the MEN1-related HPT subset, an integrated analysis of the published data may contribute to a better understanding of several critical topics and allow us to add to the list of differences between HPT/MEN1 and S-HPT (Table 5).

Treatment of MEN1

The main challenge associated with the MEN1-related HPT subset is improving the treatment options for this condition, as the recurrence rate of HPT may be as high as 50% in the period of 5–10 years after PTx (7,8,29,49). Also, the increasing survival rate of MEN1 patients may result in an increasing number of MEN1 patients with post-PTx hypoparathyroidism. Calcimimetic drugs are a potential tool that could be used to modify this outcome. HPT was controlled with 30 mg/day cinacalcet over a 12-month period in a MEN1 patient who refused a second PTx because of local recurrence, and a

Table 5 - Differences and similarities between MEN1-related HPT and sporadic HPT in terms of biochemical patterns, renal comorbidities and bone complications.

Clinical characteristic	MEN1-related HPT	Sporadic HPT
Hypercalcemia	Mildly high	Mildly/moderately high
PTH levels	Inappropriately normal or mildly high	Mildly/moderately high
PTH levels	Increasing with age	Unrelated to age
Nephrolithiasis	Higher frequency and early onset	Lower frequency
Bone mineral disease	More severe (++++)	Less severe (++)
Onset of bone disease	Early	Early
Preferentially affected bone site	Cortical bone (1/3 distal radius)	Cortical bone (1/3 distal radius)
Relative "protection" of the trabecular bone	Absent	Present
Bone outcome	Progressive (cortical and trabecular bones)	Stable (first 10 years)
Bone outcome after 10 years	Progressive (cortical)	Progressive (cortical)

MEN1: multiple endocrine neoplasia type 1. HPT: primary hyperparathyroidism.

BMD recovery at the LS (4.7%) and TH (17.8%) was seen 1 year after treatment (50). Recently, Moyes et al. documented metabolic PTH/calcium control 10–35 months after cinacalcet therapy in seven MEN1-related HPT cases (51). Despite the absence of new episodes of nephrolithiasis during the follow-up period, there was no significant BMD gain in five of the seven cases studied (51).

The current evidence shows that HPT/MEN1 is associated with a high prevalence of HPT-related comorbidities. Severe and frequent bone and renal diseases have been documented in these cases, mostly occurring in earlier but also at later stages of HPT. A better understanding of the natural history of HPT/MEN1 disease; further improvements in surgical techniques; and the development of secure, efficient, and well-tolerated calcimimetic drugs may enable more appropriate therapies to be developed for this subset of patients. It is hoped that in the near future therapeutic improvements may potentially prevent the development of bone and renal complications in HPT/MEN1 cases, correct metabolic disturbances, and avoid postsurgical hypoparathyroidism, as well as provide better management of recurrences. At present, adequate surveillance of bone, renal, and other co-morbidities in MEN1-related HPT should be performed, thereby contributing to an improved determination of the optimal timing for subtotal or total parathyroid surgery.

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AUTHOR CONTRIBUTIONS

All authors included, as this is a review article, have participated actively reviewing in detail the current literature and in the writing process of this manuscript.

REFERENCES

- Fraser WD. Hyperparathyroidism. *Lancet*. 2009;374:145–58, [http://dx.doi.org/10.1016/S0140-6736\(09\)60507-9](http://dx.doi.org/10.1016/S0140-6736(09)60507-9).
- Mosekilde L. Primary hyperparathyroidism and the skeleton. *Clin Endocrinol*. 2008;69(1):1-19, <http://dx.doi.org/10.1111/j.1365-2265.2007.03162.x>.
- DeLellis RA, Mazzaglia P, Mangray S. Primary hyperparathyroidism: a current perspective. *Arch Pathol Lab Med*. 2008;132(8):1251-62.
- Mackenzie-Feder J, Sirrs S, Anderson D, Sharif J, Khan A. Primary hyperparathyroidism: an overview. *Int J Endocrinol*. 2011;251410. Epub 2011 Jun 2.
- Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab*. 2001;86(12):5658-71, <http://dx.doi.org/10.1210/jc.86.12.5658>.
- Marx SJ, Simonds WF, Agarwal SK, Burns AL, Weinstein LS, Cochran C, et al. Hyperparathyroidism in hereditary syndromes: special expression and special managements. *J Bone Miner Res*. 2002;17:N37-N43.
- Tonelli F, Marcucci T, Fratini G, Tommasi MS, Falchetti A, Brandi ML. Is total parathyroidectomy the treatment of choice for hyperparathyroidism in multiple endocrine neoplasia type 1? *Ann Surg*. 2007;246(6):1075-82, <http://dx.doi.org/10.1097/SLA.0b013e31811f4467>.
- Stålberg P, Carling T. Familial parathyroid tumors: diagnosis and management. *World J Surg*. 2009;33(11):2234-43, <http://dx.doi.org/10.1007/s00268-009-9924-6>.
- Yip L, Ogilvie JB, Challinor SM, Salata RA, Thull DL, Yim JH, et al. Identification of multiple endocrine neoplasia type 1 in patients with apparent sporadic primary hyperparathyroidism. *Surgery*. 2008;144(6):1002-6; discussion 1006-7, <http://dx.doi.org/10.1016/j.surg.2008.07.030>
- Lourenço DM Jr, 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. *J Bone Miner Res*. 2010;25(11):2382-91, <http://dx.doi.org/10.1002/jbmr.125>.
- Thomas-Marques L, Murat A, Delemer B, Penformis A, Cardot-Bauters C, Baudin E, et al. Prospective endoscopic ultrasonographic evaluation of the frequency of nonfunctioning pancreaticoduodenal endocrine tumors in patients with multiple endocrine neoplasia type 1. *Am J Gastroenterol*. 2006;101(2):266-73, <http://dx.doi.org/10.1111/j.1572-0241.2006.00367.x>.
- Triponez F, Goudet P, Dosse D, Cougard P, Bauters C, Murat A, et al. Is surgery beneficial for MEN1 patients with small (< or = 2 cm), nonfunctioning pancreaticoduodenal endocrine tumor? An analysis of 65 patients from the GTE. *World J Surg*. 2006;30(5):654-62.
- Jorge BH, Agarwal SK, Lando VS, Salvatori R, Barbero RR, Abelin N, et al. Study of the multiple endocrine neoplasia type 1, growth hormone-releasing hormone receptor, Gs alpha, and Gi2 alpha genes in isolated familial acromegaly. *J Clin Endocrinol Metab*. 2001;86(2):542-4, <http://dx.doi.org/10.1210/jc.86.2.542>.
- Vergès B, Boureille F, Goudet P, Murat A, Beckers A, Sassolas G, et al. Pituitary disease in MEN type 1 (MEN1): data from the France-Belgium MEN1 multicenter study. *J Clin Endocrinol Metab*. 2002;87(2):457-65, <http://dx.doi.org/10.1210/jc.87.2.457>.
- Dreijerink KM, van Beek AP, Lentjes EG, Post JG, van der Luijt RB, Canninga-van Dijk MR, et al. Acromegaly in a multiple endocrine neoplasia type 1 (MEN1) family with low penetrance of the disease. *Eur J Endocrinol*. 2005;153(6):741-6, <http://dx.doi.org/10.1530/eje.1.02022>.
- Toledo RA, Lourenço DM Jr, Liberman B, Cunha-Neto MB, Cavalcanti MG, Moyses CB, et al. Germline mutation in the aryl hydrocarbon receptor interacting protein gene in familial somatotropinoma. *J Clin Endocrinol Metab*. 2007;92(5):1934-7, <http://dx.doi.org/10.1210/jc.2006-2394>.
- Toledo RA, Lourenço DM Jr, Toledo SP. Familial isolated pituitary adenoma: evidence for genetic heterogeneity. *Front Horm Res*. 2010;38:77-86, <http://dx.doi.org/10.1159/000318497>.
- Toledo RA, Mendonça BB, Fragoso MC, Soares IC, Almeida MQ, Moraes MB, et al. Isolated familial somatotropinoma: 11q13-loh and gene/protein expression analysis suggests a possible involvement of aip also in

non-pituitary tumorigenesis. *Clinics*. 2010;65(4):407-15, <http://dx.doi.org/10.1590/S1807-59322010000400010>.

19. Daly AF, Tichomirowa MA, Petrossians P, Heliövaara E, Jaffrain-Rea ML, Barlier A, et al. Clinical characteristics and therapeutic responses in patients with germ-line AIP mutations and pituitary adenomas: an international collaborative study. *J Clin Endocrinol Metab*. 2010;95(11):E373-83, <http://dx.doi.org/10.1210/jc.2009-2556>.
20. Thakker RV. Multiple endocrine neoplasia type 1 (MEN1). *Best Pract Res Clin Endocrinol Metab*. 2010;24:355-70, <http://dx.doi.org/10.1016/j.beem.2010.07.003>.
21. Costa MH, Domenice S, Toledo RA, Lourenco DM Jr, Latronico AC, Pinto EM, et al. Glucose-dependent insulinotropic peptide receptor overexpression in adrenocortical hyperplasia in MEN1 syndrome without loss of heterozygosity at the 11q13 locus. *Clinics*. 2011;66(4):529-33.
22. Lemos MC, Thakker RV. Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. *Hum Mut*. 2008;29(1):22-32, <http://dx.doi.org/10.1002/humu.20605>.
23. Toledo RA, Lourenco DM, Coutinho FL, Quedas E, Mackowiack I, Machado MC, et al. Novel MEN1 germline mutations in Brazilian families with multiple endocrine neoplasia type 1. *Clin Endocrinol (Oxf)*. 2007;67(3):377-84, <http://dx.doi.org/10.1111/j.1365-2265.2007.02895.x>.
24. Lourenço DM Jr, Toledo RA, Coutinho FL, Margarido LC, Siqueira SA, dos Santos MA, et al. The impact of clinical and genetic screenings on the management of the multiple endocrine neoplasia type 1. *Clinics*. 2007;62(4):465-76, <http://dx.doi.org/10.1590/S1807-59322007000400014>.
25. Marx SJ. Molecular genetics of multiple endocrine neoplasia types 1 and 2. *Nat Rev Cancer*. 2005;5(8):367-75, <http://dx.doi.org/10.1038/nrc1610>.
26. Dreijerink KM, Höppener JW, Timmers HM, Lips CJ. Mechanisms of disease: multiple endocrine neoplasia type 1 — relation to chromatin modifications and transcription regulation. *Nat Clin Pract Endocrinol Metab*. 2006;2(10):562-70, <http://dx.doi.org/10.1038/ncpendmet0292>.
27. Dreijerink KM, Mulder KW, Winkler GS, Höppener JW, Lips CJ, Timmers HT. Menin links estrogen receptor activation to histone H3K4 trimethylation. *Cancer Res*. 2006;66(9):4929-35, <http://dx.doi.org/10.1158/0008-5472.CAN-05-4461>.
28. Dreijerink KM, Lips CJ, Timmers HT. Multiple endocrine neoplasia type 1: a chromatin writer's block. *J Intern Med*. 2009;266(1):53-9, <http://dx.doi.org/10.1111/j.1365-2796.2009.02115.x>.
29. Burgess JR, David R, Greenaway TM, Parameswaran V, Shepherd JJ. Osteoporosis in multiple endocrine neoplasia type 1: severity, clinical significance, relationship to primary hyperparathyroidism, and response to parathyroidectomy. *Arch Surg*. 1999;134(10):1119-23, <http://dx.doi.org/10.1001/archsurg.134.10.1119>.
30. Silverberg SJ, Shane E, de la Cruz L, Dempster DW, Feldman F, Seldin D, et al. Skeletal disease in primary hyperparathyroidism. *J Bone Miner Res*. 1989;4(3):283-91, <http://dx.doi.org/10.1002/jbmr.5650040302>.
31. Parisien M, Silverberg SJ, Shane E, de la Cruz L, Lindsay R, Bilezikian JP, et al. The histomorphometry of bone in primary hyperparathyroidism: preservation of cancellous bone structure. *J Clin Endocrinol Metab*. 1990;70(4):930-8, <http://dx.doi.org/10.1210/jcem-70-4-930>.
32. Lewiecki EM, Gordon CM, Baim S, Leonard MB, Bishop NJ, Bianchi ML, et al. International Society for Clinical Densitometry 2007 adult and pediatric official positions. *Bone*. 2008;43(6):1115-21, <http://dx.doi.org/10.1016/j.bone.2008.08.106>.
33. Bilezikian JP, Khan AA, Arnold A, Brandi ML, Brown E, Bouillon R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. *J Clin Endocrinol Metab*. 2009;94(2):335-9, <http://dx.doi.org/10.1210/jc.2008-1763>.
34. Silverberg SJ, Gartenberg F, Jacobs TP, Shane E, Siris E, Staron RB, et al. Increased bone mineral density after parathyroidectomy in primary hyperparathyroidism. *J Clin Endocrinol Metab*. 1995;80(3):729-34, <http://dx.doi.org/10.1210/jc.80.3.729>.
35. Rubin MR, Bilezikian JP, McMahon DJ, Jacobs T, Shane E, Siris E, et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. *J Clin Endocrinol Metab*. 2008;93(9):3462-70, <http://dx.doi.org/10.1210/jc.2007-1215>.
36. Lourenço DM Jr, Toledo RA, Mackowiack II, Coutinho FL, Cavalcanti MG, Correia-Deur JE, et al. Multiple endocrine neoplasia type 1 in Brazil: MEN1 founding mutation, clinical features, and bone mineral density profile. *Eur J Endocrinol*. 2008;159(3):259-74, <http://dx.doi.org/10.1530/EJE-08-0153>.
37. Dempster DW, Müller R, Zhou H, Kohler T, Shane E, Parisien M, et al. Preserved three-dimensional cancellous bone structure in mild primary hyperparathyroidism. *Bone*. 2007;41(1):19-24, <http://dx.doi.org/10.1016/j.bone.2007.03.020>.
38. Norton JA, Venzon DJ, Berna MJ, Alexander HR, Fraker DL, Libutti SK, et al. 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. *Ann Surg*. 2008;247(3):501-10, <http://dx.doi.org/10.1097/SLA.0b013e31815efda5>.
39. Eller-Vainicher C, Chiodini I, Battista C, Viti R, Mascia ML, Massironi S, et al. Sporadic and MEN1-related primary hyperparathyroidism: differences in clinical expression and severity. *J Bone Miner Res*. 2009;24(8):1404-10, <http://dx.doi.org/10.1359/jbmr.090304>.
40. Kann PH, Bartsch D, Langer P, Waldmann J, Hadji P, Pfützner A, et al. Peripheral bone mineral density in correlation to disease-related predisposing conditions in patients with multiple endocrine neoplasia type 1. *J Endocrinol Invest*. 2011; Jul 27. [Epub ahead of print].
41. Coutinho FL, Lourenço Jr DM, Toledo RA, Montenegro FL, Correia-Deur JE, Toledo SP. Bone mineral density analysis in patients with primary hyperparathyroidism associated with multiple endocrine neoplasia type 1 after total parathyroidectomy. *Clin Endocrinol (Oxf)*. 2010;72(4):462-8, <http://dx.doi.org/10.1111/j.1365-2265.2009.03672.x>.
42. Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med*. 1999;341(17):1249-55, Erratum in: *N Engl J Med* 2000;342(2):144. <http://dx.doi.org/10.1056/NEJM199910213411701>.
43. Falchetti A, Marini F, Brandi ML. Multiple endocrine neoplasia type 1. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. *GeneReviews* [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2005 [updated 2010 Mar 02].
44. Lamers CBHW, Froeling PGAM. Clinical significance of primary hyperparathyroidism in familial multiple endocrine adenomatosis type I (MEA I). *Am J Med*. 1979;66:422-4, [http://dx.doi.org/10.1016/0002-9343\(79\)91062-3](http://dx.doi.org/10.1016/0002-9343(79)91062-3).
45. Christopoulos C, Antoniou N, Thempeyioti A, Calender A, Economopoulos P. Familial multiple endocrine neoplasia type I: the urologist is first on the scene. *BJU Int*. 2005;96(6):884-87, <http://dx.doi.org/10.1111/j.1464-410X.2005.05731.x>.
46. Sato M, Miyauchi A, Takahara J. Clinical aspects of hyperparathyroidism in Japanese with multiple endocrine neoplasia type 1. *Biomed Pharmacother*. 2000;54:86-9, [http://dx.doi.org/10.1016/S0753-3322\(00\)80020-7](http://dx.doi.org/10.1016/S0753-3322(00)80020-7).
47. Katai M, Sakurai A, Ikeo Y, Hashizume K. Primary hyperparathyroidism in patients with multiple endocrine neoplasia type 1: comparison with sporadic parathyroid adenomas. *Horm Metab Res*. 2001;33(8):499-503, <http://dx.doi.org/10.1055/s-2001-16944>.
48. Burgess JR, Nord B, David R, Greenaway TM, Parameswaran V, Larsson C, et al. Phenotype and phenocopy: the relationship between genotype and clinical phenotype in a single large family with multiple endocrine neoplasia type 1 (MEN 1). *Clin Endocrinol*. 2000;53(2):205-11, <http://dx.doi.org/10.1046/j.1365-2265.2000.01032.x>.
49. Goudet P, Cougard P, Vergès B, Murat A, Carnaille B, Calender A, et al. Hyperparathyroidism in multiple endocrine neoplasia type I: surgical trends and results of a 256-patient series from Groupe d'Etude des Néoplasies Endocriniennes Multiples Study Group. *World J Surg*. 2001;25(7):886-90, <http://dx.doi.org/10.1007/s00268-001-0046-z>.
50. Falchetti A, Cilotti A, Vaggelli L, Masi L, Amedei A, Cioppi F, et al. A patient with MEN1-associated hyperparathyroidism, responsive to cinacalcet. *Nat Clin Pract Endocrinol Metab*. 2008;4(6):351-7, <http://dx.doi.org/10.1038/ncpendmet0888>.
51. Moyes VJ, Monson JP, Chew SL, Akker SA. Clinical use of cinacalcet in MEN1 hyperparathyroidism. *Int J Endocrinol*. 2010;2010:906163. Epub 2010 May 26.