RESEARCH

Bone phenotypes in multiple endocrine neoplasia type 1: survey on the MEN1 Florentine database

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Abstract

Multiple endocrine neoplasia type 1 (MEN1) is a rare, inherited cancer syndrome characterized by the development of multiple endocrine and non-endocrine tumors. MEN1 patients show a reduction of bone mass and a higher prevalence of early onset osteoporosis, compared to healthy population of the same age, gender, and ethnicity. During the monitoring and follow-up of MEN1 patients, the attention of clinicians is primarily focused on the diagnosis and therapy of tumors, while the assessment of bone health and mineral metabolism is, in many cases, marginally considered. In this study, we retrospectively analyzed bone and mineral metabolism features in a series of MEN1 patients from the MEN1 Florentine database. Biochemical markers of bone and mineral metabolism and densitometric parameters of bone mass were retrieved from the database and were analyzed based on age ranges and genders of patients and presence/absence of the three main MEN1-related endocrine tumor types. Our evaluation confirmed that patients with a MEN1 diagnosis have a high prevalence of earlyonset osteopenia and osteoporosis, in association with levels of serum and urinary markers of bone turnover higher than the normal reference values, regardless of their different MEN1 tumors. Fifty percent of patients younger than 26 years manifested osteopenia and 8.3% had osteoporosis, in at least one of the measured bone sites. These data suggest the importance of including biochemical and instrumental monitoring of bone metabolism and bone mass in the routine medical evaluation and follow-up of MEN1 patients and *MEN1* carriers as important clinical aspects in the management of the syndrome.

Key Words

- multiple endocrine neoplasia type 1 (MEN1)
- bone tissue
- bone modeling
- bone turnover
- mineral metabolism
- osteoporosis

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a rare, autosomal-dominant inherited cancer syndrome characterized by the development, during the lifetime of a patient, of multiple tumors in target neuroendocrine and non-endocrine tissues, caused by germline heterozygote inactivating mutations of the *MEN1* tumor-suppressor gene.

The main affected organs are parathyroid glands, neuroendocrine cells of the gastro-entero-pancreatic tract (GEP), and the anterior pituitary. Multiple, synchronous or asynchronous, adenomas of parathyroids, resulting in primary hyperparathyroidism (PHPT), are the most common MEN1 tumors, affecting nearly 100% of patients by the age of 55 years, and the first clinical manifestation in about 90% of cases, with a mean age of onset in the third decade of life (1). Neuroendocrine tumors (NETs) of the GEP (GEP-NETs) are the second most common tumors in MEN1, affecting 30–80% of patients, with an

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age of onset of approximatively 30 years earlier than the sporadic counterpart (i.e. 10–50 vs 50–80 years), being mainly non-functioning tumors, followed by gastrinomas, insulinomas, and other extremely rare pancreatic tumors secreting somatostatin, glucagon, or vasoactive intestinal peptide (2). Functioning and non-functioning adenomas of the anterior pituitary, mainly prolactin-secreting adenoma (PRLoma), are the third most frequent manifestation of the characteristic triad of MEN1 main tumors and affect 15–55% of patients, with a mean age of onset in the fourth decade of life and a high prevalence during adolescence and early adulthood (3).

Many MEN1 tumors are functioning, over-secreting hormones that cause specific endocrine syndromes and/or can damage tissues/organs other than those directly affected by tumor.

In recent decades, some studies have shown that the premature loss of bone mass and osteoporosis represents early complications in MEN1 patients with PHPT (4, 5, 6, 7), as a consequence of prolonged periods of increased levels of parathyroid hormone (PTH) and PTH-driven bone demineralization.

Recently, Altieri *et al.* (8) reported that MEN1 patients with GEP-NETs had an increased prevalence of osteopenia and osteoporosis, mainly due to an altered nutritional status caused by excessive production of gastrointestinal hormones, medical therapy with somatostatin analogs and/or chemotherapies, and nutrient malabsorption subsequent to extensive surgical resection of duodenum and pancreas.

Functioning pituitary adenomas can concur, in MEN1 patients, with the development of an early onset secondary osteopenia and osteoporosis. Hyperprolactinemia has been associated with both increased bone formation and resorption. Over time, high levels of serum prolactin lead to an alteration of the degree of osteoclast–osteoblast coupling, resulting in bone mineral density (BMD) loss (9). ACTH-secreting adenomas cause Cushing syndrome, of which osteoporosis and increased risk of fragility fracture are well-recognized complications, as consequences of prolonged hypercortisolism (10). The hypogonadism induced by a pituitary gonadotrophic insufficiency, secondary to pituitary tumors and/or their therapy, can also represent an osteoporosis risk factor in MEN1 patients (11).

In the management of MEN1 syndrome, the main focus of clinicians is obviously on diagnosis, therapy, and follow-up of MEN1-associated tumor manifestations. Affections of bone and mineral metabolism are, in many cases, marginally investigated in MEN1 syndrome, and the assessment of bone mineral status is not commonly included in the clinical management of MEN1 patients, especially if they are not followed-up in specialized, multidisciplinary medical centers. As a Regional Referral Center for Inherited Endocrine Tumors and, at the same time, a Bone and Mineral Metabolism Hospital Unit, MEN1 patients who refer to our Center are also followed up for bone and mineral metabolism status.

Here, we performed a retrospective, observational study on bone and mineral metabolism features in a relatively wide series of MEN1 patients, based on their age and gender, and we evaluated if and how the presence of one or more of the three MEN1 main tumors could affect bone phenotype.

Materials and methods

Patients

This retrospective, observational study was performed on a series of MEN1 patients retrieved from the 'Florentine MEN1 database' (12). This clinical database is part of the 'Italian MEN1 Database' (13), which was initially approved by the Review Board of the 'Area Vasta Centro, Regione Toscana' at the 'Azienda Ospedaliera-Universitaria Careggi' (Rif. CEAVC OSS 16.234). Patients signed an informed consent form before their data were retrieved from their medical records and included in the Italian MEN1 database; their data were collected anonymously, and each patient was indicated by a unique alphanumeric code. Patients in the database were diagnosed with MEN1 based on at least one of the following criteria: (i) presence of neuroendocrine tumors in at least two of the MEN1 main affected tissues; (ii) presence of one neuroendocrine tumor in one of the MEN1 main affected tissues and one first-grade relative with MEN1; and (iii) identification of a germline-inactivating mutation of the *MEN1* gene.

From the database, we retrieved data on age, gender, clinical history of MEN1, information on MEN1-related therapies, biochemical values of serum and urinary biomarkers of bone and mineral metabolism (i.e. serum: PTH, total calcium, calcium ion, phosphorus, bone alkaline phosphatase, 25-hydroxy vitamin D; urine: calcium, phosphorus, deoxypyridinoline), BMD values (g/cm^2), T-score, and Z-score measured by dual-energy X-ray absorptiometry (DXA) (Delphi QDR Series, HOLOGIC, Marlborough, MA, USA), at lumbar spine (L1-L4), femoral neck, and total femur.

The study included MEN1 PHPT patients with either hypercalcemia or normocalcemia. Since the therapeutic

correction of PHPT is well known to normalize PTH secretion, calcemia, and mineral metabolism, and to ameliorate BMD, in this study, we included only the available biochemical values and DXA parameters measured before surgical and/or pharmacological PHPT treatment, to assess bone phenotypes in the absence of correction of PHPT. Therefore, the last biochemical and DXA measurements performed before surgery or medical therapy for PHPT were selected for the study. For patients with PHPT not treated by surgery or calcimimetics, we included the last biochemical and DXA measurements performed during their follow-up, up until March 2020.

Unfortunately, pre-operative bone metabolism-related biochemical parameters (except for serum calcium and PTH) and DXA evaluation were largely missing for a great majority of PHPT patients who underwent parathyroid surgery before 2014 and/or came to the attention of our Referral Center after parathyroidectomy had already been performed.

Based on DXA values, and according to the diagnostic criteria of the World Health Organization, patients were classified as osteoporotic if at least one of the three measured bone sites presented a score <−2.5, osteopenic with at least one score higher than −2.5 but lower than −1.0, and normal BMD if all the three measured bone sites had a score >−1.0. For this classification, T-score values (S.D. difference of patients' BMD with respect to the mean BMD value of the healthy 30-year-old reference population) were considered for men over 50 years of age and post-menopausal women, while Z-score values (S.D. difference of patients' BMD with respect to the mean BMD value of a healthy population of the same age and gender) were used for pre-menopausal women, men younger than 50 years, and children.

Statistical analysis

Biochemical and DXA parameters were calculated as mean values ± S.D. or percentages. Statistical comparisons of mean values between different groups of patients were performed by using the Student's *t*-test for parametric values, while differences in the prevalence of normal BMD, osteopenia, or osteoporosis, between different groups of patients, were analyzed using the Fisher's exact test, assuming, for both tests, a P value less than 0.05 as indicator of statistical significance (over 95%) and a P value less than 0.01 as indicator of high statistical significance (over 99%).

Results

Bone and mineral metabolism-related biochemical parameters measured before the therapeutic correction of PHPT or in subjects without PHPT were available in 101 patients (57 women and 44 men), while DXA analysis was available in 65 patients (38 women and 27 men). Demographic and tumor data of the included patients are reported in Table 1. Only tumors that had developed before biochemical and/or DXA evaluation were considered.

Biochemical parameters of bone and mineral metabolism

Bone and mineral metabolism-related biochemical parameters, stratified by the three main MEN1-associated tumors, age ranges, and genders, are reported as mean ± S.D. in Tables 2 and 3.

Patients showed generally increased levels of both the indicator of bone formation (serum bone alkaline phosphatase; BALP) and the marker of bone resorption (urinary deoxypyridinoline; DPD), independent of MEN1-associated tumors. Both the markers of bone remodeling (BALP and DPD) were higher than reference values in all three age groups, suggesting an increased bone metabolism in MEN1 patients; patients younger than 26 years presented significantly higher levels of BALP and DPD than the other two groups, indicating a greater rate of bone remodeling, associated with their younger age and with the period of achievement of the bone mass peak. No significant differences in markers of bone turnover were found between women and men, but, interestingly, women showed significantly higher serum levels of PTH in presence of the same mean value of total serum calcium and comparable values of calcium ion. Serum levels of PTH resulted increased, compared to reference values, in all three age groups but significantly higher in patients of 26–50 years and over 51 years, with respect to patients up to 25 years.

Bone mass

DXA parameters, stratified by the three main MEN1-associated tumors, age ranges, and genders, are reported as mean ± S.D. in Tables 4 and 5. The prevalence of normal BMD, osteopenia, or osteoporosis among the different groups of patients is also reported.

Patients showed a high prevalence of osteopenia, comparable in almost all the clinical subgroups,

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Table 1 Demographic characteristics of patients included in the study, stratified by occurrence of the three MEN1 main tumors.

Demographic characteristic	Total patients (n =101)	Patients with PHPT (n =76)	Patients without PHPT (n =25)	Patients with GEP-NET (n =34)	Patients without GEP-NET (n =67)	Patients with functioning pituitary adenoma (n =33)	Patients without functioning pituitary adenoma (n =68)	Patients without the three main MEN1 tumors (n =20)	Patients with only PHPT (n =30)	Patients with only GEP-NET (n = 1)	Patients with only functioning pituitary adenoma (n = 3)	Patients with PHPT and GEP-NET (n =18)	Patients with PHPT and functioning pituitary adenoma (n =14)	Patients with GEP-NET and functioning pituitary adenoma (n =1)	Patients with PHPT, GEP-NET and functioning pituitary adenoma (n =14)
Patients with bone and mineral metabolism-related biochemical parameters (n = 101)															
Age at biochemical data collection (years)	35.3 ± 16.2, range 11–80	38.3 ± 15.7, range 11–80	26.2 ± 14.5, range 11–60	40.9 ± 14.8, range 19–80	32.5 ± 16.2, range 11–74	36.0 ± 12.3, range 16–61	35.0 ± 17.8, range 11–80	22.6 ± 12.7, range 11–60	36.6 ± 17.7, range 11–74	42	40.3 ± 17.5, range 21–55	45.2 ± 15.6, range 26–80	36.0 ± 11.3, range 16–54	42	35.4 ± 13.5, range 19–61
Women (%)	57/101 (56.4)	43/76 (56.6)	14/25 (56.0)	17/34 (50.0)	40/67 (59.7)	22/33 (66.7)	35/68 (51.5)	10/20 (50.0)	20/30 (66.7)	1/1 (100)	2/3 (66.7)	5/18 (27.8)	8/14 (57.1)	1/1 (100)	10/14 (71.4)
Men (%)	44/101 (43.6)	33/76 (43.4)	11/25 (44.0)	17/34 (50.0)	27/67 (40.3)	11/33 (33.3)	33/68 (48.5)	10/20 (50.0)	10/30 (33.3)	0/1 (0)	1/3 (33.3)	13/18 (72.2)	6/14 (42.9)	0/1 (0)	4/14 (28.6)
Demographic characteristic	**Total patients (n =65)**	**Patients with PHPT (n =53)**	**Patients without PHPT (n =12)**	**Patients with GEP-NETs (n =23)**	**Patients without GEP-NETs (n =42)**	**Patients with functioning pituitary adenomas (n =22)**	**Patients without functioning pituitary adenomas (n =43)**	**Patients without the three main MEN1 tumors (n =8)**	**Patients with only PHPT (n =21)**	**Patients with only GEP-NET (n = 1)**	**Patients with only functioning pituitary adenoma (n = 2)**	**Patients with PHPT and GEP-NETs (n = 13)**	**Patients with PHPT and functioning pituitary adenomas (n = 11)**	**Patients with GEP-NETs and functioning pituitary adenomas (n = 1)**	**Patients with PHPT, GEP-NETs and functioning pituitary adenomas (n = 8)**
Patients with DXA parameters (n =65)															
Age at DXA data collection (years)	41.4 ± 16.3, range 13–79	42.9 ± 16.3, range 13–79	34.7 ± 15.5, range 15–60	45.2 ± 14.8, range 20–79	39.3 ± 16.9, range 13–73	39.1 ± 14.0, range 15–61	42.5 ± 17.4, range 13–79	31.3 ± 15.6, range 15–60	42.9 ± 18.4, range 13–73	43	41.0 ± 25.5, range 18–42	48.0 ± 15.3, range 26–79	37.9 ± 13.5, range 15–59	41	40.0 ± 15.0, range 20–61
Women (%)	38/65 (58.5)	28/53 (52.8)	10/12 (83.3)	12/23 (52.2)	26/42 (61.9)	13/22 (59.1)	25/43 (58.1)	7/8 (87.5)	12/21 (57.1)	1/1 (100)	1/2 (50.0)	5/13 (38.5)	6/11 (54.5)	1/1 (100)	5/8 (62.5)
Men (%)	27/65 (41.5)	25/53 (47.1)	2/12 (16.7)	11/23 (47.8)	16/42 (38.1)	9/22 (40.9)	18/43 (41.9)	1/8 (12.5)	9/21 (42.9)	0/1 (0)	1/2 (50.0)	8/13 (61.5)	5/11 (45.5)	0/1 (0)	3/8 (37.5)

GEP-NETs, gastro-entero-pancreatic neuroendocrine tumors; PHPT, primary hyperparathyroidism.

independent of the different MEN1 tumors (Table 4). The two subgroups of patients having only GEP-NET or only functioning pituitary adenoma had too few cases (1 and 2, respectively) to perform an effective statistical comparison of bone phenotypes and assess whether these two cancer types could, singularly, influence the health of the skeleton. Comparison between patients with or without PHPT showed no statistically significant differences in the prevalence of normal BMD ($P = 0.711$), osteopenic ($P = 0.523$), and osteoporotic ($P = 0.309$) cases between these two groups of patients. No statistically significant differences were found between patients with or without GEP-NET for the prevalence of normal BMD ($P = 0.345$), osteopenia ($P = 0.604$), and osteoporosis ($P = 0.787$). Patients with functioning pituitary tumors showed a higher prevalence of osteoporosis than those without these secreting adenomas but without reaching statistical significance ($P = 0.099$).

The high prevalence of osteopenia in at least one of the measured bone sites resulted to be a common condition in MEN1 patients, independent of their age range (Table 5). Prevalence of osteoporosis was significantly higher in the group of >51-year-old individuals, compared both to subjects of 26–50 years of age and younger than 25 years (Table 5). However, this pathological bone condition affected 25% of patients between 26 and 50 years and 8.3% of patients less than 25 years of age. The aggregate analysis of mean values of bone scores showed a progressive worsening of these parameters with aging. According to the mean value of Z-score, patients showed a normal BMD at all three bone sites only in the group of patients younger than 25 years. In the 26–50 years of age group, the mean Z-score indicated faint osteopenia at femur neck and a normal BMD at lumbar spine and total femur, while the average T-scores of patients >51 years showed lumbar osteoporosis and osteopenia of both femur sites.

No significant differences were found in lumbar spine BMD between genders, while MEN1 women showed significantly lower mean BMD value and T-score both at femoral neck and total femur (Table 5).

For 28 patients (16 women and 12 men), more than one DXA analyses were available, performed in a range of 12–113 months (mean, 36.6 ± 20.8 months) before the last DXA evaluation analyzed in this study. In 23 of these patients (82.1%), these previous DXA analyses confirmed the bone diagnosis obtained with the last DXA measurement carried out (6 normal BMD, 7 osteopenia, and 10 osteoporosis), showing no significant, positive or negative, changes overtime in BMD values and DXA scores. Four patients showed an overtime worsening of bone parameters,

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Table 2 Serum and urinary bone and mineral metabolism-related parameters, stratified by MEN1-associated tumors.

Parameter[d]	Total patients (n = 101)	Patients with PHPT (n = 76)	Patients without PHPT (n = 25)	Patients with GEP-NET (n = 34)	Patients without GEP-NET (n = 67)	Patients with functioning pituitary adenoma (n = 33)	Patients without functioning pituitary adenoma (n = 68)	Patients without the three main MEN1 tumors (n = 20)	Patients with only PHPT (n = 30)	Patients with only GEP-NET (n = 1)	Patients with only functioning pituitary adenoma (n = 3)	Patients with PHPT and GEP-NET (n =18)	Patients with PHPT and functioning pituitary adenoma (n = 14)	Patients with GEP-NET and functioning pituitary adenoma (n = 1)	Patients with PHPT, GEP-NET and functioning pituitary adenoma (n = 14)
Age at tumor diagnosis (years)	n.a.	33.0 ± 13.8	n.a.	37.0 ± 13.7	n.a.	27.5 ± 11.3	n.a.	n.a.	31.3 ± 14.9	38	32.0 ± 12.5	PHPT: 40.2 ± 12.8; GEP-NET: 39.9 ± 14.2	PHPT: 28.4 ± 10.2; Functioning pituitary adenoma: 24.1 ± 9.2	GEP-NET: 41; Functioning pituitary adenoma: 15	PHPT: 31.6 ± 13.0; GEP-NET: 32.8 ± 13.4; Functioning pituitary adenoma: 31.1 ± 12.6
Age at biochemical measurement (years)	35.3 ± 16.2	38.3 ± 15.7	26.2 ± 14.5	40.9 ± 14.8	32.5 ± 16.2	36.0 ± 12.3	35.0 ± 17.8	22.6 ± 12.7	36.6 ± 17.7	42	40.3 ± 17.5	45.2 ± 15.6	36.0 ± 11.3	42	35.4 ± 13.5
Gap between tumor development and biochemical measurement (years)	n.a.	5.3 ± 7.8	n.a.	3.9 ± 5.6	n.a.	7.8 ± 6.5	n.a.	n.a.	5.3 ± 10.3	4	8.0 ± 4.6	PHPT: 4.9 ± 6.6; GEP-NET: 5.3 ± 7.1	PHPT: 6.2 ± 6.3; Functioning pituitary adenoma: 11.9 ± 6.7	GEP-NET: 1; Functioning pituitary adenoma: 27	PHPT: 3.8 ± 3.7; GEP-NET: 2.4 ± 2.8; Functioning pituitary adenoma: 4.3 ± 4.8
Parathyroid hormone (1.3–7.6 pmol/L)	14.4[a] ± 14.1	16.4[a] ± 15.5	6.8 ± 3.1	17.0[a] ± 15.3	12.5[a] ± 13.3	18.5[a] ± 20.4	11.8[a] ± 9.1	5.9 ± 1.7	14.6[a] ± 11.1	7.8[a]	8.0[a] ± 3.4	13.6[a] ± 6.0	18.4[a] ± 22.0	10.1[a]	21.7[a] ± 22.4
Serum calcium ion (4.3–5.3 mg/dL)	5.5[a] ± 0.5	5.5[a] ± 0.5	5.6[a] ± 0.5	5.6[a] ± 0.6	5.4[a] ± 0.5	5.6[a] ± 0.5	5.4[a] ± 0.5	5.0 ± 0.4	5.7[a] ± 0.3	4.5	5.0 ± 0.3	5.5[a] ± 0.6	5.6[a] ± 0.5	5.6[a]	5.7[a] ± 0.5
Total serum calcium (8.5–10.1 mg/dL)	10.1 ± 0.9	10.4[a] ± 0.9	9.2 ± 0.6	10.3[a] ± 0.9	10.0 ± 0.9	10.2[a] ± 0.9	10.1 ± 1.0	9.3 ± 0.6	10.5[a] ± 0.8	8.2	9.4 ± 0.5	10.4[a] ± 0.9	10.2[a] ± 0.9	9.4	10.4[a] ± 0.9
Serum phosphate (2.5–4.9 mg/dL)	2.7 ± 0.8	2.5 ± 0.6	3.4 ± 1.0	2.6 ± 0.8	2.8 ± 0.8	2.4[b] ± 0.5	2.9 ± 0.9	3.5 ± 0.9	2.4[b] ± 0.7	5.6[a]	2.6 ± 0.6	2.6 ± 0.5	2.5 ± 0.4	2.6	2.2[a] ± 0.5
25-hydroxy-vitamin D (30–100 ng/mL)	22.8[b] ± 11.1	21.8[b] ± 11.3	25.6[b] ± 10.2	20.2[b] ± 12.9	24.1[b] ± 9.9	21.5[b] ± 10.5	23.5[b] ± 11.4	27.0[b] ± 8.5	22.2[b] ± 8.9	4.8[b]	26.1[b] ± 17.1	22.1[b] ± 16.2	22.7[b] ± 12.0	20.3[b]	19.0[b] ± 7.7
Bone alkaline phosphatase (Men: 7–20 µg/L; pre-menopausal women: 4–14.3 µg/L; post-menopausal women: 6–22.5 µg/L)[c]	26.9[b] ± 20.8	24.1[b] ± 14.1	33.6[b] ± 31.3	22.8[b] ± 10.2	28.9[b] ± 24.2	26.8[b] ± 18.5	27.0[b] ± 22.1	38.8[b] ± 33.7	20.8[b] ± 9.7	10.2	16.0 ± 2.9	21.7[b] ± 5.2	30.5[a] ± 23.0	17.1	26.2[a] ± 14.6
Urinary calcium (42–353 mg/24 h)	274.8 ± 163.1	325.2 ± 156.5	139.6 ± 86.5	305.8 ± 138.9	260.1 ± 172.7	335.2 ± 155.3	244.6 ± 159.8	136.2 ± 159.8	308.4 ± 173.7	66.0	120.9 ± 74.7	288.7 ± 143.6	372.5[a] ± 164.9	327.0	351.7 ± 120.7
Urinary phosphate (400–1300 mg/24 h)	747.2 ± 272.3	777.9 ± 284.9	665.1 ± 221.2	770.8 ± 290.5	737.1 ± 266.4	762.1 ± 260.4	739.5 ± 280.4	692.0 ± 247.3	775.7 ± 299.4	569.0	565.9 ± 69.2	750.9 ± 307.1	766.8 ± 256.2	628.0	835.6 ± 299.1
Urinary deoxypyridinoline (3.0–5.4 mnol/mmol creatinine)	8.0[a] ± 4.5	7.5[a] ± 3.7	9.4[a] ± 6.0	6.7[a] ± 3.1	8.6[a] ± 4.9	7.9[a] ± 3.6	8.1[a] ± 4.9	10.4[a] ± 6.5	8.1[a] ± 4.0	4.5	5.8[a] ± 1.4	5.2[a] ± 2.0	7.9[a] ± 4.1	9.4[a]	8.5[a] ± 3.5

[a]A parameter value higher than the normal range; [b]A parameter value less than the normal range; [c]Reference values for bone alkaline phosphatase from our hospital analysis laboratory are referred to adult men and adult women; [d]Referral normal values for bone and mineral metabolism biochemical parameters are indicated within brackets.
GEP-NETs, gastro-entero-pancreatic neuroendocrine tumors; n.a., not applicable; PHPT, primary hyperparathyroidism.

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Table 3 Serum and urinary bone and mineral metabolism-related parameters, stratified by age range and by gender.

Parameter[d]	Patients up to 25 years (n = 30) Group 1	Patients from 26 to 50 years (n = 52) Group 2	Patients over 51 years (n = 19) Group 3	*P* value group 1 vs group 2	*P* value group 1 vs group 3	*P* value group 2 vs group 3	Women (n = 57)	Men (n = 44)	*P* value women vs men
Age at biochemical measurement (years)	18.0 ± 4.4 Range 11–25	35.9 ± 7.4 Range 26–50	61.0 ± 8.1 Range 52–80	n.a.	n.a.	n.a.	36.0 ± 15.6	34.5 ± 17.1	Non-significant
Parathyroid hormone (1.3–7.6 pmol/L)	8.3[a] ± 4.2	18.2[a] ± 20.3	15.3[a] ± 8.6	***P* < 0.01**	***P* < 0.01**	Non-significant	17.3[a] ± 19.6	11.4[a] ± 7.5	***P* < 0.05**
Serum calcium ion (4.3–5.3 mg/dL)	5.4[a] ± 0.5	5.5[a] ± 0.5	5.5[a] ± 0.6	Non-significant	Non-significant	Non-significant	5.5[a] ± 0.6	5.4[a] ± 0.5	Non-significant
Total serum calcium (8.5–10.1 mg/dL)	10.1 ± 1.0	10.2[a] ± 1.0	9.9 ± 0.8	Non-significant	Non-significant	Non-significant	10.1 ± 1.1	10.1 ± 0.8	Non-significant
Serum phosphate (2.5–4.9 mg/dL)	3.1 ± 1.1	2.6 ± 0.7	2.6 ± 0.5	***P* < 0.05**	***P* < 0.05**	Non-significant	2.7 ± 0.8	2.8 ± 0.9	Non-significant
25-hydroxy-vitamin D (30–100 ng/mL)	25.6[b] ± 9.6	20.1[b] ± 11.0	25.1[b] ± 12.1	***P* < 0.05**	Non-significant	Non-significant	22.3[b] ± 10.7	23.4[b] ± 11.6	Non-significant
Bone alkaline phosphatase (Men: 7–20µg/L; pre-menopausal women: 4–14.3 µg/L; post-menopausal women: 6–22.5 µg/L)[c]	40.9[b] ± 31.3	21.9[b] ± 11.4	19.8 ± 8.7	***P* < 0.01**	***P* < 0.01**	Non-significant	23.3[a] ± 15.1	31.5[a] ± 25.9	Non-significant
Urinary calcium (42–353 mg/24 h)	220.1 ± 159.4	315.2 ± 164.3	254.8 ± 148.8	***P* < 0.05**	Non-significant	Non-significant	253.6 ± 159.0	299.9 ± 166.6	Non-significant
Urinary phosphate (400–1300 mg/24 h)	754.6 ± 250.3	744.6 ± 288.7	742.7 ± 265.7	Non-significant	Non-significant	Non-significant	665.3 ± 255.5	856.3 ± 258.6	***P* < 0.01**
Urinary deoxypyridinoline (3.0–5.4 mnol/mmol creatinine)	11.4[a] ± 6.3	6.8[a] ± 2.5	6.2[a] ± 2.6	***P* < 0.01**	***P* < 0.01**	Non-significant	8.3[a] ± 3.7	7.6[a] ± 5.4	Non-significant

[a]A parameter value higher than the normal range; [b]A parameter value less than the normal range; [c]Reference values for bone alkaline phosphatase from our hospital analysis laboratory are referred to adult men and adult women; [d]Referral normal values for bone and mineral metabolism biochemical parameters are indicated within brackets.
n.a., not applicable.
Parameters presenting a significant difference between different groups of patients are highlighted in bold, with $P < 0.05$ indicating a statistical significance of 95%, and $P < 0.09$ indicating a statistical significance of 99%.

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Table 4 DXA parameters, stratified by MEN1-associated tumors.

Parameter	Total patients ($n = 65$)	Patients with PHPT ($n = 53$)	Patients without PHPT ($n = 12$)	Patients with GEP-NETs ($n = 23$)	Patients without GEP-NETs ($n = 42$)	Patients with functioning pituitary adenomas ($n = 22$)	Patients without functioning pituitary adenomas ($n = 43$)	Patients without the three main MEN1 tumors ($n = 8$)	Patients with only PHPT ($n = 21$)	Patients with only GEP-NET ($n = 1$)	Patients with only functioning pituitary adenoma ($n = 2$)	Patients with PHPT and GEP-NETs ($n = 13$)	Patients with PHPT and functioning pituitary adenomas ($n = 11$)	Patients with GEP-NETs and functioning pituitary adenomas ($n = 1$)	Patients with PHPT, GEP-NETs and functioning pituitary adenomas ($n = 8$)
Age at tumor diagnosis (years)	n.a.	36.1 ± 14.8	n.a.	40.3 ± 14.3	n.a.	28.2 ± 12.5	n.a.	n.a.	34.9 ± 15.8	38	30.0 ± 17.0	PHPT: 43.2 ± 12.4; GEP-NET: 42.5 ± 14.6	PHPT: 31.3 ± 13.2; Functioning pituitary adenoma: 25.4 ± 9.2	GEP-NET: 41; Functioning pituitary adenoma: 15	PHPT: 34.8 ± 16.1; GEP-NET: 36.6 ± 15.8; Functioning pituitary adenoma: 33.4 ± 15.4
Age at DXA measurement (years)	41.4 ± 16.3	42.9 ± 16.3	34.8 ± 15.3	45.2 ± 14.8	39.3 ± 16.9	39.2 ± 13.9	42.5 ± 17.4	31.3 ± 15.6	42.9 ± 18.4	43	42.0 ± 24.0	48.0 ± 15.3	37.9 ± 13.5	41	40.0 ± 15.0
Gap between tumor diagnosis and DXA measurement (years)	n.a.	6.7 ± 9.0	n.a.	3.6 ± 3.1	n.a.	11.0 ± 8.4	n.a.	n.a.	7.5 ± 11.8	5	12.0 ± 7.1	PHPT: 5.7 ± 7.0; GEP-NET: 6.3 ± 7.7	PHPT: 6.6 ± 5.9; Functioning pituitary adenoma: 12.5 ± 9.3	GEP-NET: 0; Functioning pituitary adenoma: 26	PHPT: 5.3 ± 4.2; GEP-NET: 3.4 ± 3.7; Functioning pituitary adenoma: 6.6 ± 4.8
Lumbar spine (L1–L4) BMD (g/cm^2)	0.895 ± 0.146	0.891 ± 0.153	0.912 ± 0.117	0.897 ± 0.112	0.894 ± 0.162	0.887 ± 0.115	0.899 ± 0.161	0.911 ± 0.134	0.885 ± 0.190	0.893	0.948 ± 0.046	0.915 ± 0.139	0.886 ± 0.142	0.867	0.875 ± 0.084
Lumbar spine (L1–L4) T-score	−1.5 ± 1.4	−1.6 ± 1.4	−1.1 ± 1.0	−1.7 ± 0.9	−1.5 ± 1.6	−1.6 ± 1.2	−1.5 ± 1.5	−0.9 ± 1.2	−1.7 ± 1.8	−1.4	−1.1 ± 1.6	−1.6 ± 1.1	−1.5 ± 1.4	−1.6	−1.8 ± 0.9
Lumbar spine (L1–L4) Z-score	−1.0 ± 1.2	−1.1 ± 1.2	−0.8 ± 0.9	−1.1 ± 1.0	−1.0 ± 1.2	−1.3 ± 1.1	−0.9 ± 1.2	−0.7 ± 1.0	−1.0 ± 1.3	−1.1	−0.8 ± 1.1	−0.8 ± 1.1	−1.4 ± 1.4	−1.4	−1.5 ± 0.9
Femoral neck BMD (g/cm^2)	0.704 ± 0.118	0.709 ± 0.117	0.682 ± 0.125	0.695 ± 0.116	0.708 ± 0.121	0.726 ± 0.104	0.692 ± 0.125	0.693 ± 0.150	0.700 ± 0.119	0.666	0.691 ± 0.078	0.679 ± 0.133	0.736 ± 0.118	0.595	0.584 ± 0.864
Femoral neck T-score	−1.6 ± 0.9	−1.6 ± 0.9	−1.7 ± 0.9	−1.7 ± 0.9	−1.6 ± 0.9	−1.3 ± 0.9	−1.8 ± 0.9	−1.6 ± 1.0	−1.7 ± 0.9	−1.6	−1.6 ± 0.9	−1.9 ± 0.9	−1.2 ± 0.9	−2.3	−1.3 ± 1.1
Femoral neck Z-score	−1.1 ± 0.8	−1.0 ± 0.8	−1.4 ± 0.8	−0.9 ± 0.9	−1.1 ± 0.8	−0.9 ± 0.8	−1.2 ± 0.8	−1.4 ± 1.0	−1.2 ± 0.6	−1.3	−1.1 ± 0.2	−1.0 ± 0.9	−0.8 ± 0.9	−2.0	−0.7 ± 0.8
Total femur BMD (g/cm^2)	0.830 ± 0.167	0.842 ± 0.176	0.782 ± 0.123	0.844 ± 0.176	0.821 ± 0.163	0.857 ± 0.113	0.814 ± 0.191	0.781 ± 0.146	0.805 ± 0.201	0.758	0.833 ± 0.083	0.855 ± 0.222	0.876 ± 0.117	0.717	0.739 ± 0.092
Total femur T-score	−1.3 ± 1.0	−1.2 ± 1.0	−1.5 ± 0.8	−1.2 ± 0.9	−1.3 ± 1.0	−0.9 ± 0.9	−1.5 ± 0.9	−1.5 ± 0.9	−1.5 ± 1.0	−1.5	−1.1 ± 0.9	−1.3 ± 1.0	−0.8 ± 0.9	−1.8	−1.3 ± 1.1
Total femur Z-score	−0.9 ± 0.9	−0.8 ± 0.9	−1.2 ± 0.8	−0.8 ± 1.0	−1.0 ± 0.9	−0.7 ± 0.8	−1.0 ± 0.9	−1.2 ± 1.0	−1.1 ± 0.8	−1.3	−0.9 ± 0.6	−0.8 ± 1.2	−0.7 ± 0.9	−1.7	−0.5 ± 0.8
Normal BMD value (%)	14/65 (21.5)	11/53 (20.8)	3/12 (25.0)	3/23 (13.0)	11/42 (26.2)	7/22 (31.8)	7/43 (16.3)	2/8 (25.0)	3/21 (14.2)	0/1 (0)	1/2 (50.0)	2/13 (15.4)	5/11 (45.5)	0/1 (0)	1/8 (12.5)
Osteopenia (%)	30/65 (46.2)	23/53 (43.4)	7/12 (58.3)	12/23 (52.2)	18/42 (42.8)	11/22 (50.0)	19/43 (44.2)	4/8 (50.0)	9/21 (42.9)	1/1 (100)	1/2 (50.0)	5/13 (38.5)	4/11 (36.6)	1/1 (100)	5/8 (62.5)
Osteoporosis (%)	21/65 (32.3)	19/53 (35.8)	2/12 (16.7)	8/23 (34.8)	13/42 (31.0)	4/22 (18.2)	17/43 (39.5)	2/8 (25.0)	9/21 (42.9)	0/1 (0)	0/2 (0)	6/13 (46.1)	2/11 (18.2)	0/1 (0)	2/8 (25.0)

GEP-NETs, gastro-entero-pancreatic neuroendocrine tumors; n.a., not applicable; PHPT, primary hyperparathyroidism.

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Table 5 DXA parameters, stratified by age range and by gender.

Parameter	**Patients up to 25 years** ($n = 12$); **group 1**	**Patients from 26–50 years** ($n = 32$); **group 2**	**Patients over 51 years** ($n = 21$); **group 3**	***P* value group 1 vs group 2**	***P* value group 1 vs group 3**	***P* value group 2 vs group 3**	**Women** ($n = 38$)	**Men** ($n = 27$)	***P* value women vs men**
Age at DXA measurement (years)	19.5 ± 4.3; range 13–25	36.9 ± 6.9; range 26–50	60.7 ± 7.4; range 51–79	n.a.	n.a.	n.a.	40.4 ± 16.6	42.7 ± 16.0	Non-significant
Lumbar spine (L1–L4) BMD (g/cm^2)	0.968 ± 0.131	0.937 ± 0.132	0.779 ± 0.108	Non-significant	***P* <0.01**	***P* <0.01**	0.872 ± 0.140	0.930 ± 0.151	Non-significant
Lumbar spine (L1–L4) T-score	−0.4 ± 1.5	−1.3 ± 1.1	−2.6 ± 0.9	***P* < 0.05**	***P* <0.01**	***P* <0.01**	−1.5 ± 1.3	−1.5 ± 1.4	Non-significant
Lumbar spine (L1–L4) Z-score	−0.4 ± 1.5	−1.0 ± 1.1	−1.5 ± 0.9	Non-significant	Non-significant	Non-significant	−1.0 ± 1.0	−1.1 ± 1.4	Non-significant
Femoral neck BMD (g/cm^2)	0.778 ± 0.117	0.721 ± 0.115	0.626 ± 0.079	Non-significant	***P* <0.01**	***P* <0.01**	0.669 ± 0.100	0.759 ± 0.125	***P* <0.01**
Femoral neck T-score	−1.0 ± 0.9	−1.5 ± 0.9	−2.2 ± 0.6	Non-significant	***P* <0.01**	***P* <0.01**	−1.8 ± 0.9	−1.4 ± 0.9	***P* <0.05**
Femoral neck Z-score	−1.0 ± 0.9	−1.1 ± 0.9	−1.1 ± 0.4	Non-significant	Non-significant	Non-significant	−1.3 ± 0.7	−0.8 ± 0.8	Non-significant
Total femur BMD (g/cm^2)	0.849 ± 0.153	0.849 ± 0.190	0.785 ± 0.129	Non-significant	Non-significant	Non-significant	0.756 ± 0.107	0.946 ± 0.181	***P* <0.01**
Total femur T-score	−1.0 ± 1.0	−1.2 ± 1.0	−1.6 ± 0.7	Non-significant	***P* < 0.05**	Non-significant	−1.6 ± 0.9	−0.8 ± 0.9	***P* <0.01**
Total femur Z-score	−1.0 ± 1.0	−0.9 ± 1.0	−0.9 ± 0.7	Non-significant	Non-significant	Non-significant	−1.1 ± 0.8	−1.1 ± 0.8	Non-significant
Normal BMD value (%)	5/12 (41.7)	10/32 (31.2)	0/21 (0)	Non-significant	***P* < 0.01**	***P* < 0.01**	7/38 (18.4)	7/27 (25.9)	Non-significant
Osteopenia (%)	6/12 (50.0)	14/32 (43.8)	9/21 (42.9)	Non-significant	Non-significant	Non-significant	16/38 (42.1)	14/27 (51.9)	Non-significant
Osteoporosis (%)	1/12 (8.3)	8/32 (25.0)	12/21 (57.1)	Non-significant	***P* <0.01**	***P* < 0.05**	15/38 (39.5)	6/27 (22.2)	Non-significant

n.a., not applicable.

Parameters presenting a significant difference between different groups of patients are highlighted in bold, with $P < 0.05$ indicating a statistical significance of 95%, and $P < 0.09$ indicating a statistical significance of 99%.

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passing from a diagnosis of osteopenia to osteoporosis in an average time of 38.3 ± 20.9 months. Only one patient, a male over the age of 50 years, showed an improvement of lumbar spine T-score (from -2.5 to -2.2), passing from a diagnosis of osteoporosis to osteopenia, in two different DXA measurements performed at a time distance of 20 months. Conversely, both the femur sites showed a slight worsening of T-score (from -2.1 to -2.2 at femur neck and from -1.5 to -1.7 at total femur). Interestingly, this patient had not yet developed either PHPT or GEP-NET at the times of both DXA measurements, and he had only a PRL-secreting microadenoma, diagnosed 7 years before the first DXA analysis and under constant pharmacological therapy with cabergoline. This patient was treated with an annual infusion of zoledronic acid from the time of the densitometric finding of osteoporosis, which improved lumbar BMD.

Data on the occurrence of atraumatic or low-trauma fractures were available in the medical records for only three patients: (i) an osteoporotic man referring to the occurrence of spontaneous rib fracture twice, at the age of 45 and 55 years. No DXA data were available at the times of fracture; the first available DXA analysis was 4 years after the second fracture event, showing osteoporosis at lumbar spine with a T-score of -2.9 and osteopenia at femur neck with a T-score of -2.1; (ii) a young man with a low-trauma fracture of the distal epiphysis of the radial bone at 25 years, in presence of a DXA evaluation performed the same year of fracture occurrence, showing severe osteoporosis with Z-scores of -4.4 and -2.7 at lumbar spine and at femur neck, respectively; and (iii) a young woman with a low-trauma fracture of the right ulnar apophysis at 22 years. A DXA evaluation performed 1 year before fracture occurrence showed normal bone mass at lumbar spine (Z-score ±0.2), femur neck (Z-score -0.5), and total femur (Z-score -0.1).

Discussion

Early onset reduction of bone mass appears to be a common hallmark in patients with MEN1 syndrome, as a consequence of the development of MEN1-related functioning neuroendocrine tumors and overexpression of specific hormones that alter bone and mineral metabolism and, if released during adolescence and early adulthood, affect skeletal modeling and achievement of bone mass peak. In our series of patients, either the marker of bone formation (BALP) or the indicator of bone resorption (DPD) resulted to be increased, with respect to reference values, in patients under the age of 51 years, independently of MEN1 tumor(s), indicating an accelerated bone turnover in these patients. These two markers resulted to be increased in both women and men, with no significant differences between the two genders. In patients less than 25 years of age, this accelerated bone metabolism could be ascribed, at least in part, to normal skeleton modeling, while in patients between 26 and 50 years, it appears to be the consequence of altered hormonal regulation of mineral metabolism caused by MEN1 tumors. A direct effect of the *MEN1* gene mutation on osteoblast and osteoclast activity cannot be excluded.

Deficiency or insufficiency of vitamin D is among the factors that can concur to alter correct bone remodeling and bone mass acquisition and maintenance. All our MEN1 patients with serum levels of 25-hydroxy-vitamin D less than 20.0 ng/mL (deficiency) received constant supplementation of this hormone. Despite this supplementation, on average, our MEN1 patients had levels of 25-hydroxy vitamin D less than 30.0 ng/mL, independent of their age range or gender. This persistent insufficiency could be due to the fact that over 75% of the cases have PHPT, and MEN1 PHPT usually has a long, asymptomatic, normocalcemic course, during which the elevated levels of PTH can 'consume' 25-hydroxy vitamin D by converting it into 1,25-dihydroxy vitamin D, which would explain the insufficient values of serum 25-hydroxy vitamin D we evidenced in our population, possibly concurring to alter bone and mineral metabolism.

Four previous studies (4, 5, 6, 7) reported an early occurrence of bone mass loss and a high prevalence of osteopenia and osteoporosis in MEN1 patients with PHPT, with respect to the general population of the same age and gender. In accordance with these findings, our MEN1 PHPT patients had osteopenia and osteoporosis in 43.4 and 35.8% of cases, respectively. Moreover, our study, performed in a relatively higher number of cases, also including non-PHPT MEN1 patients, showed a global prevalence of osteopenia in almost half of the patients (46.2%) and osteoporosis in almost one in three cases (32.3%), both appearing to be independent of the MEN1-associated tumor(s). Interestingly, no significant differences were evidenced in spine and femur Z- and T-scores between patients with or without PHPT, as well as in the prevalence of normal BMD, osteopenic, and osteoporotic cases among these two groups of patients, suggesting that in MEN1 patients, an excess of PTH is not the only cause of increased bone turnover and premature loss of bone mass, as previously shown by Kann *et al.* (11).

The eight MEN1 patients who had not yet clinically manifested MEN1 had mean T- and Z-scores indicating

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osteopenia at femur neck, a site predominantly composed of cortical bone, while T- and Z-scores at lumbar spine, mainly consisting of trabecular bone, indicated a normal bone. Five of them had normal serum values of PTH and total calcium and one presented a borderline PTH level and normal serum calcium. Two women were normocalcemic with an occasionally faintly increased PTH value, and instrumental evidence of no parathyroid lesion, one having osteopenia at lumbar spine and osteoporosis at the femur and one with osteopenia at both spine and femur. At the time of the last available DXA evaluation, these eight patients had a mean age of 31.3 years; five were younger than 28 years and three were aged respectively 41, 42, and 60 years. The reduction of bone mass at femur sites, but not at lumbar spine, at young age, with respect to the normal population of the same age and gender, in the absence of any recognized MEN1-associated functioning tumors or significantly altered biochemical hormone values could indicate a possible direct role of the *MEN1* gene mutation in cortical bone remodeling. An *in vivo* study by Kanazawa *et al.* (14) on a mouse model with the conditional inactivation of the *Men1* gene in mature osteoblasts showed a detrimental effect of menin loss on BMD value, cortical bone thickness, and structure, number, and volume of trabeculae that all resulted to be significantly reduced with respect to control littermates, in association with significantly increased structure model index, trabecular thickness, and trabecular separation.

Interestingly, the three MEN1 patients older than 28 years who are still clinically unaffected are a mother and her two daughters, who bear the p.Cys354Phe missense mutation in the exon 8 of the *MEN1* gene. The cysteine to phenylalanine substitution at position 354 affects a central domain of menin protein presumably involved in the interaction with JunD (15), a component of the AP-1 transcription factor. WT menin represses AP-1 transcription activity, by directly binding to JunD (15). JunD has been shown to suppress bone formation and contribute to reduction of bone mass. Repression of JunD, such as that induced by menin, resulted in expression of markers of osteoblast activity, such as Runx2, osteocalcin, and collagen type 1 (16). Therefore, we can speculate that in MEN1 patients with a *MEN1* mutation disrupting the negative control of menin on JunD, the genetic defect could be directly responsible for bone mass loss by JunD-mediated reduction of osteoblast activity, independent of the presence of MEN1 tumor(s). On the other hand, given the fact that all these three patients have not yet developed endocrine or non-endocrine MEN1-associated tumors or manifested significantly altered biochemical hormone values, we can speculate that their point non-truncating mutation could be a low-penetrance *MEN1* mutation for MEN1 tumorigenesis and/or that they have other, unknown, genetic or epigenetic factors, which may exert a 'protective' effect on the phenotypical development of MEN1 syndrome and related clinical manifestations.

When we analyzed only patients over 35 years of age, we found a reduction of the prevalence of osteopenia (46.2–43.9%) and an increase in the prevalence of osteoporosis (32.3–41.5%) with respect to our entire MEN1 population. Our aggregated data of osteopenia and osteoporosis prevalence in all patients over 35 years (males and females), independent of their MEN1 tumor(s), were in agreement with those of Burgess *et al.* (4), although his study included only MEN1 women with PHPT. Conversely, when we analyzed only women, our data showed a higher prevalence of osteoporosis (54.5% vs 45%) and a lower prevalence of osteopenia (36.4% vs 41%) with respect to the Burgess study (4).

As for the general population, in our MEN1 patients, the female gender showed a higher prevalence of osteoporosis, both in the group of patients over 35 years (54.5% in women vs 26.3% in men) and in the entire MEN1 population (39.5% in women vs 22.2% in men) but without reaching statistical significance. Bone mass value at the lumbar spine site showed no difference between genders while, at femur neck, women presented a significantly lower T-score.

Age was confirmed to be the main cause of bone loss, even in our MEN1 population, with a progressive worsening of bone scores at spine and femur neck, in the three analyzed age groups, as occurs in the general population, and a 57.1% of osteoporosis prevalence in patients over 51 years.

As demonstrated by previous studies (4, 17), including a recent one from our Research Group performed on the MEN1 Florentine database (18), in MEN1 PHPT patients, parathyroidectomy is effective in normalizing PTH, serum calcium levels, and biochemical parameters of bone resorption and bone formation, as well as in blocking the premature loss of bone mass and improving BMD. Hypercalcemia is normally the main indication for parathyroid surgery. However, in case of normocalcemic MEN1 PHPT, recurrent renal diseases (nephrolithiasis/nephrocalcinosis) and/or early onset loss of bone mass and increased risk of fragility fracture may be an indication for earlier surgical intervention. Considering the results of the present study, which confirm that patients with a MEN1 diagnosis have a high prevalence of osteopenia that manifests before 25 years of age (50% of cases), and of early

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onset osteoporosis from the age of 26 years, it would be of clinical interest to include regular evaluation of mineral metabolism and bone mass in the context of routine medical monitoring of MEN1 patients and *MEN1* carriers, starting from adolescence, as these are important clinical aspects for the management of the syndrome.

In the opinion of the authors, the instrumental assessment of bone status, as well as the fracture risk scores (i.e. FRAX), should be a part of the clinical evaluation of MEN1 patients and *MEN1* carriers. In addition to DXA BMD evaluation, the use of high-resolution peripheral quantitative CT (HRpQCT), a three-dimensional, non-invasive, low-radiation imaging modality with superior sensitivity for assessing cortical and trabecular bone indices (i.e. geometry, volumetric density, and microstructure), and early detection of bone loss, changes, and abnormalities, could provide additional information on volumetric BMD and microarchitecture of cortical and trabecular compartments of the distal tibia and distal radius (the latter a site of prevalent cortical bone, particularly affected in patients with PHPT (19)), and be, thus, of valuable utility for an early and routine monitoring of bone health in MEN1 patients.

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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