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Clinical Research Article

Tumor-induced Osteomalacia: A Systematic Review and Individual Patient's Data Analysis

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Abstract

Context: Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome, usually caused by small, benign, and slow-growing phosphaturic mesenchymal tumors. Clinically, TIO is characterized by renal phosphate leak, causing hypophosphatemia and osteomalacia. This review was performed to assess the clinical characteristics of TIO patients described worldwide so far.

Evidence Acquisition: On June 26, 2021, a systematic search was performed in Medline, Google Scholar, Google book, and Cochrane Library using the terms: "tumor induced osteomalacia," "oncogenic osteomalacia," "hypophosphatemia." There were no language restrictions. This review was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses criteria.

Evidence Results: Overall, 1725 TIO cases were collected. TIO was more frequent in adult men, who showed a higher incidence of fractures compared with TIO women. The TIO-causing neoplasms were identified in 1493 patients. The somatostatin receptor-based imaging modalities have the highest sensitivity for the identification of TIO-causing neoplasms. TIO-causing neoplasms were equally located in bone and soft tissues; the latter showed a higher prevalence of fractures and deformities. The surgery is the preferred TIO definitive treatment (successful in > 90% of patients). Promising nonsurgical therapies are treatments with burosumab in TIO patients with elevated fibroblast growth factor-23 levels, and with radiolabeled somatostatin analogs in patients with TIO-causing neoplasm identified by somatostatin receptor-based imaging techniques.

Conclusion: TIO occurs preferentially in adult men. The TIO clinical expressiveness is more severe in men as well as in patients with TIO-causing neoplasms located in soft tissues. Treatments with burosumab and with radiolabeled somatostatin analogs are the most promising nonsurgical therapies.

Key Words: tumor induced osteomalacia, oncogenic osteomalacia, phosphaturic mesenchymal tumors, renal phosphate leak, hypophosphatemia

Abbreviations: 18^F, ^{18}fluorine; 25OHD, 25 hydroxyvitamin D; ^{68}Ga, ^{68}gallium; ^{177}Lu, ^{177}lutetium; CT, computed tomography; FDG, fluorodeoxyglucose; FGF, fibroblast growth factor; IPD, individual patient data; MEPE, matrix extracellular phosphoglycoprotein; MRI, magnetic resonance imaging; OR, odds ratio; PET, positron emission tomography; PMT, phosphaturic mesenchymal tumor; SPECT, single-photon emission computed tomography; TIO, tumor-induced osteomalacia; T_mPO_4/GFR, tubular phosphate reabsorption threshold normalized for glomerular filtration rate

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is an uncommon paraneoplastic syndrome biochemically characterized by a renal phosphate leak causing severe hypophosphatemia (< 0.8 mmol/L), normal serum levels of calcium, PTH, and 25 hydroxyvitamin D (25OHD), and low or inappropriately normal $1,25(OH)_2D$ serum levels (1). The renal phosphate leak is defined by a tubular phosphate reabsorption threshold normalized for glomerular filtration rate ($TmPO_4$/GFR) < 0.7 mmol/mmol (2). Clinically, TIO is characterized by debilitating muscle weakness, bone pain, pathological fractures and/or pseudo-fractures, and bone deformities. Instrumentally, TIO patients show a significant reduction of bone mineral density evaluated by dual-energy X-ray absorptiometry. Altogether, these clinical, biochemical, and instrumental signs define TIO-related osteomalacic syndrome (1).

TIO is usually caused by phosphaturic mesenchymal tumors (PMTs). The PMTs are usually small, benign, and slow-growing polymorphous neoplasms (3), affecting bone or soft tissues, that secretes fibroblast growth factor 23 (FGF23) and, rarely, other phosphatonins (ie, secreted frizzled-related protein-4, FGF7, and matrix extracellular phosphoglycoprotein [MEPE]) (1, 4). The overproduction of FGF23 and other phosphatonins decreases the renal tubular phosphate reabsorption, causing the renal phosphate loss and the significant hypophosphatemia (5). The TIO causing neoplasm identification may be challenging for the conventional anatomy-based imaging techniques like computed tomography (CT) or magnetic resonance imaging (MRI) because of the small dimension and the highly variable anatomical location. In addition, the local symptoms directly related to PMT

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are frequently overshadowed by the severe systemic symptoms of TIO-related osteomalacic syndrome (6).

To the best of our knowledge, no systematic analysis has been performed of the clinical characteristics of all TIO cases described worldwide. The present work is a systematic review based on TIO-related information published in peer-reviewed scientific journals.

Materials and Methods

Data Sources and Search Strategy

This systematic review was planned, conducted, and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (7).

A systematic search of the medical literature was performed in Medline, Google Scholar, Google book, and Cochrane Library (last conducted search June 26, 2021) using the following terms: "tumor-induced osteomalacia," "oncogenic osteomalacia," "hypophosphatemia." There were no language restrictions. The reference lists of all identified articles were searched for further relevant publications.

Study Selection

Eligible studies were case reports, cases series, and review articles. The review articles were selected for this study to evaluate the state of the art and to find articles through the bibliography that could not be found at the first research. Because it is likely that the individual case reports delivered earlier were included as part of subsequent case series published by the same authors, all articles were acquired as full text and the references were analyzed to tease out duplicate data. Predetermined inclusion criteria were patients of all ages with TIO clinical diagnosis. Exclusion criteria were patients of all ages with diagnosis of primary hyperparathyroidism, Fanconi syndrome, and genetic disorders of phosphate homeostasis (8).

Data Extraction

Titles and abstracts (when available) of the studies retrieved using the described search strategy were screened independently by 2 review team members (V.A. and G.C.) to identify studies that potentially met the inclusion criteria outlined. The full text of potentially eligible studies was retrieved and independently assessed for eligibility by 4 review team members (D.R., G.D.F., A.C., and P.S.). Selected studies in language other than English, French, and Italian (ie, Chinese, Russian, Spanish, Portuguese, German, Hungarian, and Japanese) were translated into English or Italian by a specialist translator. Any disagreement over the eligibility of studies was resolved through discussion between all review team members. A standardized, prepiloted form was used to extract relevant clinical data from the included studies. The extracted information included gender, age at TIO diagnosis, age at onset of TIO-related symptoms, symptoms related to TIO, biochemical data at TIO diagnosis and after treatment, imaging tests, diagnostic instrumental tests, TIO neoplasm localization, histological characteristics of TIO tumor whenever described, type of treatment, survival status, date of last follow-up, or death. Two review team members (V.A. and G.C.) extracted data independently, discrepancies were identified and resolved through discussion with D.R. and G.D.F. When available, missing data were obtained on request from study authors.

The risk of bias of the studies included in the systematic review was assessed according to established criteria of Quality Assessment of Diagnostic Accuracy Studies 2 (9) and reported in Supplementary Table 1 (10).

Statistical Analysis

All statistical analyses were performed by L.D.E. using the IBM SPSS (Statistical Package for Social Science), version 25 (IBM, Armonk, NY, USA). Data from study publications were extracted and included in a single database. These data then were reanalyzed and combined. Because the distribution of continuous variables was not normal, nonparametric Mann-Whitney test was used to analyze between-group differences. The χ^2 or Fisher exact tests were used to evaluate differences between categorical variables or proportions. Data were expressed as absolute number, percentage, or 50th percentile (25th-75th percentile), as appropriate. The risk of specific outcomes was estimated by binary logistic regression analysis including categorical variables as covariates and expressed as odds ratio (OR) (95% CI). The sensitivity of the tests was calculated by the following formula: number of true positives/(number of true positives + number of false negatives). All statistical tests were 2-tailed. A P value < 0.05 was considered statistically significant.

Results

The databases search led to the identification and screening of 664 studies. After the exclusion of studies not meeting the inclusion criteria, 451 studies were included in qualitative and quantitative syntheses (Fig. 1) and they are reported in Supplementary document 1 (11). The case reports and the case series included in the final analysis were 320 and 131, respectively.

Characteristics of TIO Patients

A total of 1725 patients with TIO were identified. TIO was diagnosed in 843 men (55%) and 689 women (45%). Data regarding sex were missing in 193 TIO subjects. This series includes 10 patients referred to the Department of Clinical Medicine and Surgery of the Federico II University in Naples, Italy, from January 1979 to June 2021. Although only 5 of these patients were described in a previous publication (12), the clinical data of all the 10 patients referred to the Department of Clinical Medicine and Surgery have been included in this review.

The serum phosphate levels in all patients were 0.48 (0.42-0.54) mmol/L, the $TmPO_4$/GFR was 0.38 (0.28-0.46) mmol/mmol, the serum C-term FGF23 levels were 448 (231-954) RU/mL, and the serum intact FGF23 levels were 215 (123-395) pg/mL. Of interest, serum FGF23 levels were within the normal range in 2 TIO patients, and the authors suggest that the secretion of phosphatonins other than FGF23 should be taken into account in the pathogenesis of TIO in these patients (13, 14). Simultaneously elevated circulating levels of FGF7 and FGF23 have been also described in 1 TIO patient (15).

Table 1 summarizes the clinical and biochemical features of TIO patients and shows that the affected men had a higher incidence of bone fractures (OR = 1.16; 1.04-1.30), higher serum alkaline phosphatase levels, and lower serum PTH levels compared with women.

Table 1. Clinical and biochemical characteristics of TIO patients by sex

	No.	Men	Women
Number, n; %	1532	843; 55.0	689; 45.0
Age at TIO onset, y	1010	39.0 (33.0-48.0)	39.0 (35.9-50.0)
Age at TIO diagnosis, y	1499	45.0 (39.0-54.0)	44.0 (39.0-56.0)
Clinical signs and symptoms	1252	700; 55.9	552; 44.1
Weakness, n; %		388; 55.4	284; 51.4
Pain, n; %		544; 77.7	427; 77.4
Functional impairment, n; %		246; 35.1	197; 35.7
Bone fractures, n; %		393; 56.1[a]	266; 48.2
Pseudofractures, n; %		39; 5.6	28; 5.1
Deformities, n; %		88; 12.6	70; 12.7
Biochemical parameters			
Serum calcium, mmol/L	921	2.26 (2.20-2.33)	2.26 (2.18-2.33)
Serum phosphate, mmol/L	1182	0.48 (0.42-0.54)	0.48 (0.42-0.53)
Serum ALP, %	655	237 (174-300)[a]	222 (153-280)
PTH, mmol/L	794	7.12 (4.69-9.00)[a]	7.31 (5.53-9.84)
25OHD, mmol/L	523	48.0 (39.0-72.0)	48.0 (38.9-74.9)
$1,25(OH)_2D$, nmol/L	606	37.9 (25.4-48.0)	37.5 (25.4-48.0)
$TmPO_4$/GFR, mmol/mmol	648	0.38 (0.26-0.47)	0.39 (0.28-0.47)
C- term FGF23, RU/mL	327	448 (237-1065)	448 (230-918)
Intact FGF23, pg/mL	466	208 (112-395)	279 (123-395)

The data were expressed as 50th (25th-75th percentile) and as absolute; percentage number for continuous and categorical variables, respectively.
Abbreviations: Age at TIO onset, age at first presentation of TIO-related osteomalacic syndrome; ALP, total alkaline phosphatase, expressed as percentage values compared with upper limit of the laboratory reference range; C-term FGF23, C-terminal FGF23 diagnostic assay; FGF23, fibroblast growth factor 23; intact FGF23, intact FGF23 diagnostic assay; pain, chronic bone pain; TIO, tumor-induced osteomalacia; $TmPO_4$/GFR, renal threshold of phosphate concentration normalized for glomerular filtration rate ; weakness: muscle weakness.
[a]Significantly different compared with women with TIO.

Tumor Localization

The TIO-causing tumor was identified in 1493 subjects within an average of 4.0 (2.0-6.0) years from the onset of osteomalacic syndrome. In 73 patients, the TIO-causing tumor was not identified despite extensive diagnostic efforts. The differences between patients in whom the TIO-causing neoplasm was identified and those in whom the attempts to localize it failed are reported in Table 2. Patients in whom the TIO-causing neoplasm was identified were younger, reported more frequent bone pain, and showed lower serum phosphate, higher serum calcium, and higher serum levels of intact FGF23 at onset of osteomalacic syndrome compared with patients in whom the TIO-causing neoplasm was not identified. The TIO-causing neoplasms were detected by positron emission tomography (PET)-CT with ^{68}gallium (^{68}Ga) (345; 32.2%), OctreoScan (206; 19.2%), MRI (123; 11.5%), PET-CT with ^{18}fluorine (^{18}F) fluorodeoxyglucose (FDG) (89; 8.3%), CT (84; 7.8%), technetium-99m methylene diphosphonate bone scintigraphy (81; 7.6%), physical examination (72; 6.7%), radiograph (31; 2.9%), flexible fiberoptic endoscopy (17; 1.6%), selective venous samplings for FGF23 (14; 1.3%), ultrasound (6; 0.6%), ^{18}F-AIF-NOTA-octreotide (10; 0.9%), and bone scintigraphy (8; 0.7%). Altogether, systemic venous sampling for FGF23 was used in 32 patients. The clinical and biochemical characteristics of these patients are reported in Supplementary Table 2 (16). Of interest, the serum phosphate levels resulted lower in patients with a diagnostic systemic venous sampling for FGF23, similar to Andreopoulou's findings (17).

The sensitivity analysis indicates that hybrid imaging with ^{99m}Tc HYNIC-TOC single-photon emission CT (SPECT)-CT and ^{68}Ga-DOTATOC PET-CT had better sensitivity compared with all other techniques (Table 3).

When a tumor was not found, the diagnostic modalities adopted were physical examination (73; 100%), PET-CT with ^{18}FDG (48; 65.8%), OctreoScan (46; 63.0%), CT (35; 47.9%), MRI (35; 47.9%), PET-CT with ^{68}Ga-DOTATOC (33; 45.2%), radiograph (9; 12.3%), bone scintigraphy (9; 12.3%), systemic venous samplings for FGF23 (5; 6.8%), and ultrasound (1; 1.4%).

Table 4 summarizes the distribution of TIO-causing neoplasms in the body according to sex. Overall, the TIO-causing neoplasms were more frequently located in the lower limbs (639; 53.2%) and in the head (363; 30.2%). The localization in the lower limbs was more common in men (OR 1.33 [1.06-1.67]), whereas the one in the head was more frequent among women (OR 1.44 [1.24-1.84]). However, the gender distribution ratio for tumors localized in head and neck region was equal in men (146; 49.8%) and in women (147; 50.2%), confirming data already reported by Shah et al (18).

Table 5 summarizes the clinical and biochemical characteristics of TIO patients according to localization of the TIO-causing neoplasm in bone vs soft tissues. The overall prevalence of TIO-causing neoplasm in soft and bone tissue was similar. TIO patients with neoplasm localization in bone tissue showed higher 25OHD serum levels compared with patients with neoplasm localization in soft tissues. The latter, on the other hand, showed a higher risk of bone fractures (OR 1.32; 1.05-1.67]), functional impairment (OR 1.56; 1.22-2.00]), and deformities (OR 2.39; 1.65-3.46]) compared with TIO patients with neoplasm located in bone tissue.

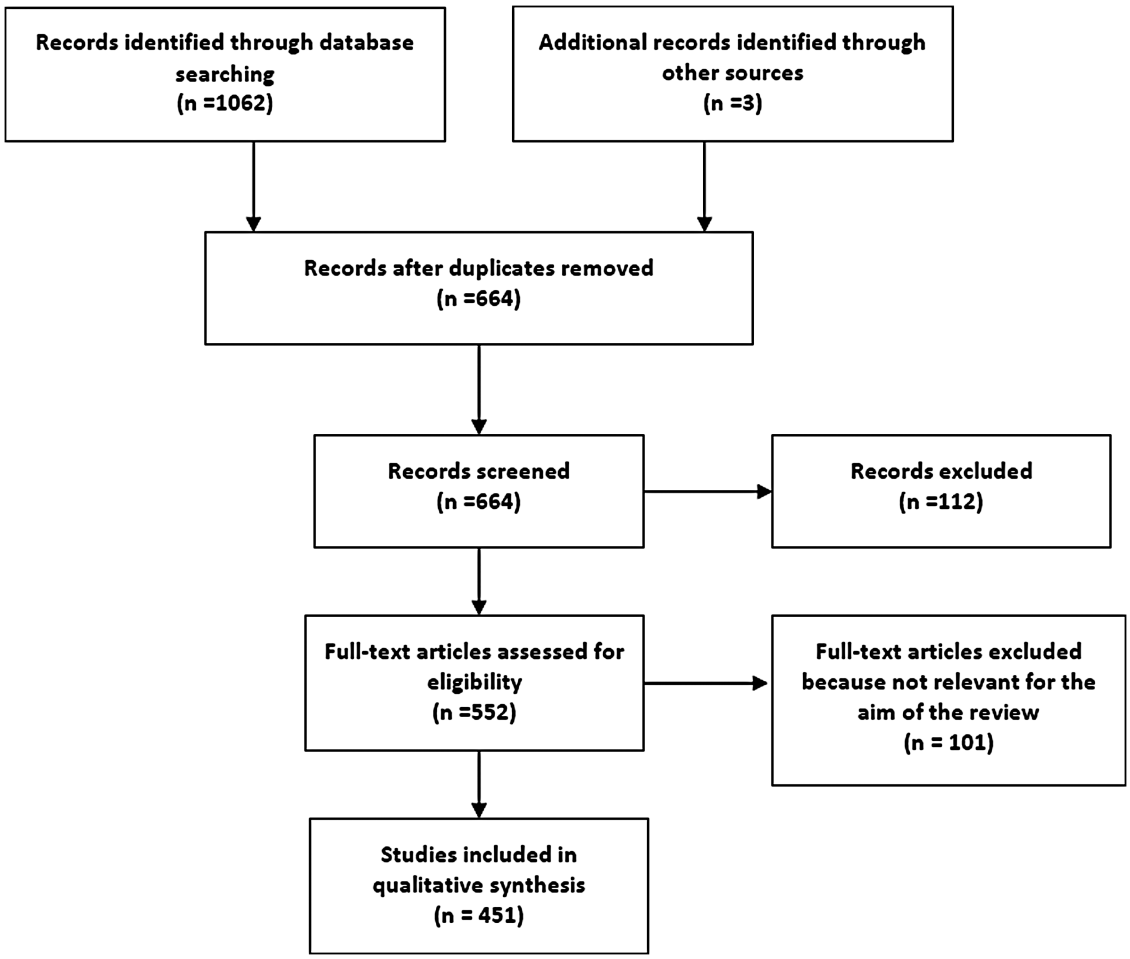

Figure 1. PRISMA flow chart of the study.

Histological Data

Histological data were described in 1223 subjects: of them, 977 (79.9%) had PMTs; 110 (9.0%) had hemangiopericytomas; 28 (2.3%) had benign bone tumors, ossifying fibromas, enchondromas, chondroblastoma; 28 (2.3%) had giant cell tumors; 12 (1.0%) had nerve sheath tumors, such as schwannoma and glomangiopericytoma; 12 (1.0%) had benign skin tumor, such as fibrous histiocytomas, lipomas, and angiomyolipomas; 11 (0.9%) had odontogenic tumor; 9 (0.7%) had osteosarcoma; 6 (0.5%) had prostatic adenocarcinomas; 6 (0.5%) had soft-tissue sarcomas; 5 (0.4%) had parathyroid adenomas; 5 (0.4%) had lung tumors, among them 2 (0.2%) had small-cell cancers and 3 (0.2%) had non-small-cell cancers; 4 (0.3%) had kidney tumors, of whom 2 (0.2%) had squamous cell carcinomas, 1 (0.1%) had a hypernephroma and 1 (0.1%) had a papillary adenoma; 3 (0.2%) had breast tumors; 2 (0.2%) had neuroendocrine tumors; 2 (0.2%) had hematological malignancies; 1 (0.2%) a papillary thyroid tumor; 1 (0.1%) an uterine fibroma; and 1 (0.1%) a melanoma.

Of interest, immunohistochemistry demonstrated high expression of FGF23 and MEPE, at transcriptional and translational levels, in TIO tumors, in particular in hemangiopericytomas and in giant cell tumor (19, 20).

Management of Tumor-induced Osteomalacia

Data regarding TIO management were available in 1070 subjects. When the tumor was identified, surgical treatment was proposed to 1000 patients: 987 (98.7%) of them were surgically treated. Thirteen patients (1.3%) refused surgical treatment. In 57 patients, the surgical procedure was considered impossible or was not resolutive (5.5%). Various therapies alternative or adjuvant to surgery were attempted: burosumab was administered in 28 patients (2.8%) with high serum FGF23 levels; somatostatin analogs in 11 patients (1.1%) with a positive OctreoScan; radiotherapy in 10 patients (1.0%), of whom 2 refused surgical procedures and in all the others cases the radiotherapy was proposed as adjuvant therapy; chemotherapy in 10 patients (1.0%), of whom 4 were diagnosed with a malignant TIO, 2 were diagnosed with hematological malignancies and 1 was diagnosed with a multifocal TIO; radioablation in 9 patients (0.9%), that presented the TIO-causing neoplasm in the lower limbs, 5 in soft tissues and 4 in bones; cinacalcet in 8 (0.8%), of whom 3 patients received the drug when the tumor was not identified; cryoablation in 3 (0.3%), which presented the TIO-causing neoplasm in bone tissue of lower limbs; embolization in 3 (0.3%), which presented the TIO-causing neoplasm in bone tissue; radiolabeled ^{177}lutetium (^{177}Lu)-DOTATATE in 3 patients (0.3%) with a positive PET-CT with ^{68}Ga-DOTATOC.

When the TIO-causing neoplasm was not identified or the treatment adopted was unsuccessful, the conservative therapy was based on oral administration of calcitriol (dosage between 1.0 and 3.0 μg/d) and phosphate salts (mean dosage, 2.0 g/d) in patients with TIO-related osteomalacic syndrome associated with serum FGF23 levels elevated or

Table 2. Clinical and biochemical characteristics of TIO patients according to the identification of the causal neoplasms

		TIO-causing neoplasm	
	No.	Identified	Not Identified
Number, n; %	1566	1493; 95.3	73; 4.7
Men: women, n; %	1383	731; 55.4: 588; 44.6	35; 54.6: 29; 45.4
Age at TIO onset, y	962	39.0 (34.0-48.0)[a]	48.0 (34.5-58.0)
Age at TIO diagnosis, y	1376	44.0 (39.0-54.0)	50.0 (33.0-60.0)
Clinical signs and symptoms	1272	1224; 96.2	48; 7.7
Weakness, n; %		629; 51.4	26; 54.2
Pain, n; %		985; 80.5[a]	27; 56.3
Functional impairment, n; %		417; 34.1	11; 22.9
Bone fractures, n; %		606; 49.5	18; 37.5
Pseudofractures, n; %		64; 5.2	3; 6.3
Deformities, n; %		150; 12.3	6; 12.5
Biochemical parameters			
Serum calcium, mmol/L	885	2.26 (2.20-2.33)[a]	2.19 (2.10-2.30)
Serum phosphate, mmol/L	1090	0.48 (0.42-0.54)[a]	0.56 (0.48-0.70)
Serum ALP, %	639	224 (164-286)	170 (131-293)
PTH, mmol/L	763	7.12 (5.03-9.01)	7.79 (3.66-12.50)
25OHD, mmol/L	491	48.0 (39.0-68.8)	71.1 (37.3-96.5)
1,25OH_2D, nmol/L	595	37.9 (25.4–48.0)	48.0 (27.0-75.7)
$TmPO_4$/GFR, mmol/mmol	569	0.38 (0.28-0.44)	0.45 (0.24-0.58)
C-term FGF23, RU/mL	301	450 (238-945)	441 (160-832)
Intact FGF23, pg/mL	386	314 (123-395)[a]	146 (37-280)

The data were expressed as 50th (25th-75th percentile) and as absolute; percentage number for continuous and categorical variables, respectively.
Abbreviations: C-term, C-terminal FGF23 diagnostic assay; age at TIO onset, age at first presentation of TIO-related osteomalacic syndrome; ALP, total alkaline phosphatase, expressed as percentage values compared with upper limit of the laboratory reference range; FGF23. fibroblast growth factor 23; identified, patients in whom the TIO-causing neoplasm has been found; intact: intact FGF23 diagnostic assay; not identified, patients in whom the TIO-causing neoplasm has not been found; pain, chronic bone pain; TIO, tumor-induced osteomalacia; $TmPO_4$/GFR, normalized renal threshold phosphate concentration; weakness, muscle weakness.
[a]Significantly different compared with patients with not identified TIO-causing neoplasm.

Table 3. Sensitivity analysis of diagnostic procedures used for detection of TIO-causing neoplasms

Diagnostic methodology	No.	Sn	95% CI
^{99m}HYNIC TOC SPECT-CT	92	0.92	0.88-0.98
^{68}Ga DOTATOC PET/CT	274	0.91	0.88-0.94
US	80	0.79	0.70-0.88
Octreoscan	347	0.76	0.72-0.80
MRI	435	0.71	0.67-0.76
CT	372	0.69	0.62-0.75
^{18}F-FDG PET/CT	229	0.68	0.62-0.74
Rx	225	0.20	0.14-0.25
Tc-99m MDP bone scintigraphy	154	0.10	0.14-0.25
Physical examination	1142	0.10	0.08-0.11

Abbreviations: ^{18}F-FDG PET/CT, fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography; ^{68}Ga DOTATOC PET/CT, ^{68}Gallium DOTATOC positron emission tomography/computed tomography; ^{99m}HYNIC TOC SPECT-CT, technetium-99m HYNIC-TOC single-photon emission computed tomography; CT, computed tomography; MRI, magnetic resonance imaging; Octreoscan, 111in-pentetreotide scintigraphy; Rx, radiography; Sn, sensitivity; Tc-99m MDP bone scintigraphy, technetium-99m methylene diphosphonate bone scintigraphy; TIO, tumor-induced osteomalacia; US, ultrasound.

inappropriately normal related to hypophosphatemia (1, 21). Burosumab and calcitriol treatment were not recommended in patients with TIO-related osteomalacic syndrome not associated with increased FGF23 (1, 22). Cholecalciferol treatment was also given to correct 25OHD deficiency, based on criteria validate for the general population (1). This pharmacological treatment significantly improves clinical symptoms TIO related (1, 12).

Follow-up

Considering the newly available therapeutic tools for TIO, we suggest considering the normalization of serum phosphate levels (defined as phosphate serum levels within the normal range of each laboratory) as TIO remission and the normalization of serum phosphate and FGF23 levels (the latter defined as FGF23 serum levels within the normal range of each FGF23 assay kit) as TIO resolution.

TIO remission was observed in 818 patients. Among them, 699 patients (84.9%) have undergone surgical procedures (rate of success = 94.8%), 13 (1.6%) have been treated with burosumab (rate of success = 92.9%), 7 (0.9%) with radiotherapy (rate of success = 77.8%), 5 (0.6%) with radioablation (rate of success = 83.3%), 4 (0.5%) with somatostatin analogs (rate of success = 40%), 3 (0.4%) with chemotherapy (rate of success = 75%), 2 (0.2%) with embolization (rate of success = 100%), 2 (0.2%) with cryoablation (rate of success = 100%), 2 (0.2%) with cinacalcet (rate of success = 100%), and 1 (0.1%) with radiolabeled ^{177}Lu-DOTATATE (rate of success = 100%). In 70 patients (8.5%), the normalization of serum phosphate levels was obtained with administration of calcitriol and phosphate (rate of success = 86.4%).

Data regarding TIO resolution were available in 207 patients. Of these, 152 (73.4%) had undergone surgical procedures, 4 (1.9%) had been treated with radiotherapy, 3 (1.4%) with radioablation, 2 (1.0%) with chemotherapy, 2 (1.0%) with cryoablation, 2 (1.0%) with radiolabeled ^{177}Lu-DOTATATE, and 1 (0.5%) with embolization.

Follow-up time information was available in 769 TIO patients. The median follow-up period being 7.20 (1.80-12.75) years.

By the end of follow-up, 39 patients (5.1%) had died for TIO-related causes. Patients who died during the follow-up were older at TIO clinical onset (57.5 [46.5-72.5] vs 39.0 [33.0-53.0] years, $P < 0.04$), and at TIO diagnosis (56.5 [38.3-68.0] vs 45.0 [38.3-53.0] years, $P < 0.04$) and presented with serum alkaline phosphatase levels at diagnosis (303 [145-1043] vs 222 [177-266] %, $P < 0.04$) compared to survivors. Six-hundred and sixty-two patients (90.7%) stayed asymptomatic until the end of the follow-up time.

Table 4. Body distribution of TIO-causing neoplasm by sex

	Men (n = 661)	Women (n = 548)
Head, n; %	177; 26.7[a]	186; 34.4
Shoulder, n; %	7; 1.1	6; 1.1
Upper limb, n; %	35; 5.3	30; 5.6
Chest, n; %	43; 6.5	38; 7.0
Abdomen, n; %	26; 3.9	22; 4.1
Lower limb, n; %	373; 56.3[a]	266; 49.3

The data are expressed as absolute; percentage number.
Abbreviation: TIO, tumor-induced osteomalacia.
[a]Significantly different compared with women.

Multifocal TIO-causing Neoplasm

Multifocal TIO-causing neoplasms were described in 6 patients (Supplementary Table 3) (23). Compared with patients with unifocal TIO, patients with multifocal TIO showed no difference in clinical and biochemical parameters, except for a higher risk of pseudofractures (OR = 9.1; 1.6-50.9; $P < 0.04$). The tumors were located in the bone in 4 patients (66.6%)

Table 5. Clinical and biochemical characteristics of TIO patients according to tissue in which the TIO-causing neoplasm is located

		TIO-causing neoplasm location	
	n°	Bone	Soft tissue
Number, n; %	1382	681; 49.3	701; 50.7
Age at TIO onset, y	1302	38.8 (32.0-48.0)	39.0 (35.9-48.0)
Age at TIO diagnosis, y	1103	45.0 (38.0-54.0)	43.2 (40.8-54.0)
Clinical signs and symptoms	1146	555; 48.4	591; 51.6
Weakness, n; %		287; 51.7	328; 55.5
Pain, n;		438;79.0	465; 78.7
Functional impairment, n; %		170; 30.6[a]	238; 40.3
Bone fractures, n; %		266; 47.9[a]	325; 55.0
Pseudofractures, n; %		24; 4.3	39; 6.6
Deformities, n; %		45; 8.1[a]	103; 17.4
Biochemical parameters			
Serum calcium, mmol/L	811	2.25 (2.17-2.33)	2.26 (2.20-2.32)
Serum phosphate, mmol/L	998	0.48 (0.41-0.56)	0.48 (0.42-0.51)
Serum ALP, %	609	222 (158-287)	238 (171-286)
PTH, mmol/L	680	7.31 (4.80-9.72)	7.12 (5.17-8.09)
25OHD, mmol/L	442	48.5 (39.0-73.7)[a]	44.5 (37.6-60.0)
1,25 OH_2 D, nmol/L	537	37.4 (25.4-48.0)	37.9 (25.4-44.9)
$TmPO_4$/GFR, mmol/mmol	538	0.38 (0.28-0.45)	0.39 (0.26-0.44)
C-term FGF23, RU/mL	266	448 (260-948)	484 (232-945)
Intact FGF23, pg/mL	350	249 (123-419)	314 (123-385)

The data were expressed as 50th (25th-75th percentile) and as absolute; percentage number for continuous and categorical variables, respectively.
Abbreviations: age at TIO onset, age at first presentation of TIO-related osteomalacic syndrome; ALP, total alkaline phosphatase, expressed as percentage values compared to upper limit of the laboratory reference range; bone, TIO patients in whom the TIO-causing neoplasm has been found in bone tissue; FGF23, fibroblast growth factor 23; FGF23 C-term, C-terminal FGF23 diagnostic assay; FGF23 intact, intact FGF23 diagnostic assay; pain, chronic bone pain; soft tissue, TIO patients in whom the TIO-causing neoplasm has been found in any other tissue different from bone; TIO, tumor-induced osteomalacia; $TmPO_4$/GFR, renal threshold phosphate concentration normalized for glomerular filtration rate; weakness, muscle weakness.
[a]Significantly different compared with TIO patients in whom the TIO-causing neoplasm has been found in any other tissue different from bone.

and in soft tissues in 2 (33.3%). All the tumors were resected by surgery, and histological features were consistent with a diagnosis of PMT. Normalization of serum phosphorus levels was obtained in all patients, whereas normalization of serum FGF23 was obtained in 66.7% of patients No patient died before the end of follow-up.

Malignant TIO

Malignant TIO was considered as the tumor's ability to cause metastasis or giving local recurrence (24). Malignant TIOs were observed in 67 patients, of whom 35 were male (52.2%) and 32 were female (47.8%). Of interest, malignant neoplasms were associated with a higher risk of pseudofractures (OR = 4.5; 1.6-12.9; $P < 0.04$). In addition, patients with malignant TIO showed lower $TmPO_4$/GFR (0.38; 0.25-0.44 vs 0.43; 0.37-0.48 mmol/mmol; $P < 0.04$) and higher calcium serum levels (2.29; 2.17-2.37 vs 2.25; 2.23-2.28 mmol/L; $P < 0.04$) compared with patients without.

Data regarding histology were available in 58 patients with malignant TIOs. Of these, 40 (70.2%) had PMT, 5 (8.8%) hemangiopericytomas, 4 (5.6%) lung tumor, 2 (3.5%) prostatic adenocarcinomas, 2 (3.5%) giant cell tumors, 2 (3.5%) squamous cell carcinomas of the kidney, 1 (1.8%) melanoma, 1 (1.8%) osteosarcoma, and 1 (1.8%) soft-tissue sarcoma.

Thirty-nine (68.4%) patients were surgically treated, 9 (15.8%) patients were medically treated with phosphate salts and calcitriol, 4 (7.0%) patients received chemotherapy, 2 (5.0%) patients radiotherapy, 1 (1.8%) patient cryoablation, 1 (1.8%) patient radioablation, and 1 (1.8%) radiolabeled ^{177}Lu-DOTATATE. Data regarding treatment were missing in 10 patients.

Normalization of serum phosphate levels was obtained in 30 (71.4%) patients during the follow-up. In 9 patients (47.4%), the normalization of serum FGF23 levels was obtained, whereas 10 (52.6%) patients with malignant TIO died during the follow-up for causes linked to TIO.

Discussion

Although a systematic review of all published TIO cases limited to head and neck region as well as a summary of all pediatric TIO patients has been previously published (18, 25), comprehensive individual patient data (IPD) analysis of all TIO patients has not yet been done: we believe therefore that ours is the first such systematic review about clinical features, diagnostic tools, and therapeutic intervention in all patients with TIO published to date. Our analysis demonstrated that a sexual dimorphism is apparent in the TIO clinical expression, with TIO being more frequent in men than in women. Male TIO patients showed a preferential localization of the TIO-causing neoplasm in the lower limbs and had a higher prevalence of fractures compared with women, who in turn had a preferential localization of TIO-causing neoplasm in the head. The review confirmed that almost 80% of all TIO cases are caused by small, benign, and slow-growing PMTs located in soft or in bone tissues. However, one can argue that the TIO tumor labeled as other than PMT are often the cases of missed findings of typical PMT, according to Folpe (3).

Of interest, epidemiological surveys indicate that the mesenchymal tumors such as PMTs affect men more often than women across a wide age range (26). The precise reason for such findings, especially the site preference of lower limbs in men and head in women, is not known. This difference may be linked to the physiological process of sexual differentiation (27). Lee and colleagues identified a novel *FN1-FGFR1* fusion gene in a significant percentage of PMTs. This fusion gene encodes for a chimeric protein that contributes to PMTs development through autocrine and paracrine pathways (28). In both human and experimental models, *FGFR1* and *FN1* showed a preferential expression in men. This evidence was obtained by evaluating the expression of the *FGFR1* gene in subjects affected by colon-rectal cancer: in this setting, the *FGFR1* gene is more frequently transcribed in men than in women (29). Moreover, in an animal model, the expression of the *Fn1* gene is significantly influenced by an epigenetic mechanism involving dietary habits and sex (30).

Our results also indicate that the TIO-causing neoplasms were preferentially identified in patients with a more severe clinical expression of the osteomalacic syndrome. In accordance with our findings, Pal and colleagues reported that TIO neoplasm' size positively correlated with serum FGF23 levels (31). Higher FGF23 levels result in more severe hypophosphatemia, which in turn causes chronic bone pain (32). Probably the highest detectability of TIO-causing neoplasms in subjects with more severe expression of the osteomalacic syndrome is related to a larger tumor size. Also, it is apparent that patients with identified TIO-causing neoplasms were younger at onset of symptoms than patients without identified TIO-causing neoplasms, whereas age at diagnosis of TIO was not different between the 2 groups, as reported in Table 2. In other words, the former group had longer duration of symptomatology before diagnosis of TIO was made. Higher serum FGF23, lower serum phosphate levels, and the occurrence of more symptoms could then be considered a consequence of longer duration of disease. This implies that patients without identified TIO-causing neoplasms, if followed long enough, do have a chance of having their tumor detected over time.

Also, TIO-causing neoplasms located in soft and bone tissues showed a different clinical expression. In particular, TIO-causing neoplasms located in soft tissue are associated with more severe clinical expression of osteomalacic syndrome (higher incidence of fractures, deformities, and muscular impairment) compared with patients with TIO-causing neoplasms located in bone. Although the precise reason is not known, this phenomenon can be linked to the different anatomopathological features and behaviors, observed and reported by Folpe, between PMTs located in soft tissue and those located in bone tissue (3). The bone PMTs, indeed, grow in a preexisting trabeculae, show an endocrine pattern of growth, and produce on rare occasions calcified, osteoid-like matrix. On the other hand, soft-tissue PMTs tend to infiltrate into surrounding tissues and reveal a richly vascularized stroma (3).

Our findings suggest that, once the diagnosis of TIO has been established, a stepwise approach to imaging should be used to identify the TIO-causing neoplasm. This should start with fusion imaging technique to detect potential PMTs followed by anatomical imaging in areas of major uptake for more precise tumor localization and characterization for surgery (33). In this context, the technology of somatostatin-receptor functional scintigraphy markedly facilitates the localization of TIO tumor. A recent meta-analysis performed by Jiang and coworkers indicated that somatostatin receptor-based imaging modalities outperformed ^{18}F-FDG PET-CT in the detection of TIO, with ^{68}Ga-DOTA-SST PET-CT

performing slightly better than OctreoScan-SPECT-CT (34). These data have been confirmed by our IPD analysis. When the neoplasm cannot be located by a fusion imaging technique, FGF23 venous concentration ratio between the venous drainage of the tumor bed in comparison to the general circulation can be taken into account to locate the area of the body where the tumor is presumably located, assuming that the responsible tumor is the major or only source of hormone in the given patient (35). However, the fusion imaging technique and systemic venous samplings for FGF23 were adequately used in a significant percentage of TIO patients in whom the causing neoplasm was not identified. The unidentified TIO cases are an important clinical entity that could be etio-pathologically related to phosphatonins different from FGF23, such as FGF7, MEPE, secreted frizzled-related protein-4, and dentin matrix protein 1. Regarding unidentified TIOs, we hope that in the future the role of these other phosphatonins will be better clarified. In this regard, data reported by some authors are very interesting (15, 19, 20).

An important aspect is represented by multifocal TIO. Our study indicated that patients with multifocal TIO show a higher risk of pseudofractures and a rate of relapse higher than 30%.

During the diagnostic process, calcitriol and phosphate salts currently are the standard therapy to efficiently control the TIO-related osteomalacic syndrome. Phosphate supplementation can lead over time to secondary hyperparathyroidism and possibly tertiary hyperparathyroidism if the therapy is maintained for a long time (36). The risk of this adverse effect is reduced by administering calcitriol and by regular monitoring of magnesium and 25OHD status. Indeed, a normal magnesium serum levels can help to control secondary hyperparathyroidism giving its ability to inhibit PTH secretion and up-regulate the calcium sensing receptor, vitamin D receptor, and FGF receptor/Klotho (37). On the other hand, if overzealous therapy is continued for a long time, 1 consequence is the development of hypercalciuria, which can in turn lead to nephrocalcinosis or nephrolithiasis with the further contribution of hyperphosphaturia (38).

For these reasons, regular follow-up is mandatory in patients undergoing this medical treatment in order to tailor the therapy on each patient. We suggest quarterly evaluations of serum levels of PTH, 25OHD, creatinine, calcium, phosphate, albumin, and magnesium, as well as of 24-hour urinary excretion of calcium, creatinine, and phosphate.

When the TIO-causing neoplasm is located and is amenable to operation, surgery is by and large the treatment of choice. Attention should be paid to remove the neoplasm with wide margins (1) because TIO can persist even if small amounts of the tumor tissue remain; furthermore, local relapse, multifocality, and/or distant metastasis may occur, as shown by our review. Historically, both radiotherapy and chemotherapy have been used as adjuvant and/or primary therapy in case the TIO-causing neoplasm cannot be surgically treated. After the demonstration of the uptake of radiolabeled somatostatin analogs by PMTs, the administration of radiolabeled somatostatin receptor-based therapies, such as octreotide (33) and the ^{177}Lu-DOTATATE, have been proposed (39, 40).

Additional promising therapies that have been used in TIO cases are the administration of cinacalcet or burosumab. Both these treatments have been used in TIO patients with FGF23-mediated renal phosphate leak and hypophosphatemia. Cinacalcet acts by allosteric activation of the calcium sensing receptor, the main negative regulator of PTH secretion. Cinacalcet induces a functional hypoparathyroidism that, in turn, decreases renal phosphate wasting and increases serum phosphate levels (41). Burosumab is a fully human anti-FGF23 antibody that inhibits the FGF23 biological actions ameliorating phosphate homeostasis in TIO patients (42). In patients with TIO-causing neoplasms located in the lower limbs who refuse surgical procedures or when surgery is considered as demolitive, radioablation can be taken into account considering the high cure rate (43).

In TIO patients undergoing potentially resolutive treatment, prudentially, serum FGF23 levels should be evaluated in addition to all the other biochemical parameters suggested here in the follow-up strategy, in agreement with Minisola and colleagues (1). When the biochemical profile of these patients suggests a TIO relapse, it would be useful to assess if these were due to an incomplete removal or a multifocal TIO, with a persistence of FGF23 elevation (1).

The IPD analysis used in this study has several limitations as well as advantages. It allows the gathering of a large amount of heterogeneous data through the inclusion of all trials, minimizing the selective reporting bias. It thus represents the best opportunity to summarize the results of multiple studies (44, 45). On the downside, the heterogeneous medical database can also limit the clinical value of such kind of study because it can only summarize individual data. In addition, particular attention must be paid to the analysis of the patients' data described in more than 1 article.

In summary, this systematic review showed that TIO presents with more severe clinical symptoms and signs in men, as well as in patients with TIO-causing neoplasm located in bone tissue. It also confirms that the somatostatin receptor-based imaging modalities have the highest sensitivity for the identification of TIO-causing neoplasms. Surgery is definitely the preferred treatment of TIO; surgically treated patients showing a rate of healing > 90%. The promising nonsurgical therapies are treatments with burosumab in FGF23-related osteomalacic syndrome, and with radiolabeled somatostatin analogs in patients with the causing neoplasm identified by somatostatin receptor-based imaging technique. Given the challenging diagnostic and treatment management, we suggest TIO patients to be referred to third-level specialized care center.

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This in an unfunded study.

Disclosures

D.R. has previously consulted for Kyowa Kyrin. All other authors have nothing to declare.

Data Availability

All datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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