

Research article

Difficulties in decision making on a long standing, complicated case of osteoporosis – a real challenge for functional rehabilitation

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Abstract: We aim was to present a case of severe osteoporosis with concern to an adult female who was under specific medication against the condition while she experienced inexplicable weight loss in association with an incidental fracture inconsistent with DXA changes. Challenges of the case management and decision making are further on explained. Real-life-medicine poses multiple issues that require an individual decision while respecting the standard protocols. That is why a generalized decision is rather impractical. Here we introduce the clinical case of a lady in her late 60s with a known 6-year history of osteoporosis that required several difficult decisions along surveillance: at first, zoledronic acid represented an available solution, yet after one year, BMD decreased and adjustment was done by initiating a second sequence according to the teriparatide protocol. DXA-BMD, as well as the spectrum of bone turnover markers, qualified the patient as responsive and she further continued with oral bisphosphonates while being monitored *via* telemedicine amid COVID-19 pandemic. After 24 more months, a second decision of zoledronic acid was done, despite prior partial response, but digestive complains restricted the oral administration of anti-osteoporotic drugs. After one more year, denosumab was initiated and consecutive follow-up is essential. At this point, another challenging aspect was revealed: the discordance between DXA – based scores increase and the presence of an incidental fracture. A supplementary investigation was considered useful (Tc- whole body scintigraphy) noting the clinical presentation with local pain, dysfunctionality, and mild weight loss that also required rehabilitation management.

Keywords: DXA, osteoporotic fracture, rehabilitation, pain, surgery, anti-resorptive, teriparatide, zoledronate, weight loss

Introduction

Sequential therapy against menopause - and age - related osteoporosis represents a long standing challenge due to disease burden, long term impact of both the condition, but, also, the medication, the association with other morbidities and required drugs with potential complications (such as, for instance, glucocorticoids therapy for autoimmune conditions, etc.); this aspect overall represents a complex multidisciplinary perspective and an associated rehabilitation plan is mandatory to be implemented in daily life [1-3].

The treatment gap includes a heterogeneous panel that takes into consideration the access to specific regimes, the patients' compliance to long term medication, the spectrum of expected side effects, and, also, the skills of the practitioners that take care of one individual diagnosed with this disorder from guidelines implementation to personalized medicine; of note, osteoporosis and fragility fractures display an increasing incidence amid modern era, the future projections remaining dramatic from the point of view of affected people despite the fact that a consistent segment of population actually is and will be still under-diagnosed, and thus not adequately treated [4-6].

The current widely used options (in addition to the life style intervention, including calcium and vitamin D replacements, physical exercise, keeping an active life, daily sun exposure, etc.) are anti-resorptives such as bisphosphonates and denosumab and anabolic drugs against osteoporosis, mostly teriparatide; the sequence of choosing one drug instead of another, prioritizing the safety and efficacy, represents sometimes a difficult decision in daily practice that should not overlook the medical and social issues, as well [7-9].

1. Results

Table 1. DXA scans (GE Lunar Prodigy) in relationship with the medical therapy against osteoporosis

Year	DXA region	T-score (SD)	BMD (g/sqcm)	Z-score (SD)	Therapy
6 years prior	lumbar L1-4 *	0.745	-3.6	-1.9	Zoledronic acid 5 mg i.v.
5 years prior	lumbar L1-4	0.677	-4.1	-2.1	Teriparatide 20 µg/day s.c.
	total hip	0.695	-2.5	-1.0	
	femoral neck	0.690	-2.4	-1.0	
	radius **	0.488	-3.2	-2.1	
4 years prior	lumbar L1-4	0.823	-3.0	-1.0	After 12 months of teriparatide
	total hip	0.690	-2.5	-1.1	
	femoral neck	0.673	-2.6	-0.9	
	radius **	0.515	-2.8	-1.6	
3 years prior	lumbar L1-4	0.747	-3.5	-1.5	After 24 months of teriparatide → switch to alendronate p.o. 5600/week for 2 years ***
	total hip	0.699	-2.5	-0.9	
	femoral neck	0.718	-2.3	-0.5	
	radius **	0.525	-2.6	-1.4	
1 year prior	lumbar L1-L4	0.703	-3.9	-1.7	Zoledronic acid 5 mg i.v.
	total hip	0.747	-2.1	-0.4	
	femoral neck	0.734	-2.2	-0.3	
	radius **	0.644	-2.7	-1.1	
current admission	lumbar L1-4	0.836	-2.9	-0.7	Denosumab s.c. 60 mg every 6 months
	total hip	0.734	-2.2	-0.6	
	femoral neck	0.717	-2.2	-0.3	
	radius **	0.688	-2.1	-0.5	

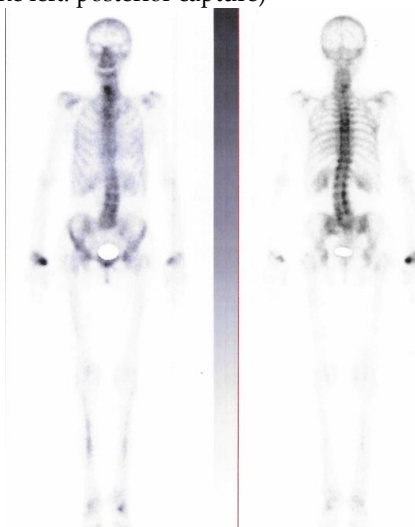
Abbreviations: DXA=Dual-Energy X-Ray Absorptiometry; SD=standard deviation; BMD=bone mineral density; i.v.=intravenous; p.o.=oral; s.c.=subcutaneous; *other DXA regions were not explored; ** third distal area of the radius at non-dominant forearm; *** these 2 years of alendronate overlapped to the first 2 years of COVID-19 pandemic; the blue box represents 24-month teriparatide protocol

Table 2. Blood bone turnover markers profile under long standing medication against osteoporosis

Year	Osteocalcin (N: 15-46) ng/mL	CrossLaps (N: 0.33- 0.782) ng/mL	P1NP (N: 20.25- 76.31) ng/mL	Alkaline phosphatase (N: 40-150) U/L	Therapy
6 years prior	15.00	0.33	35	65	Zoledronic acid 5 mg i.v.
5 years prior	12.00	0.19	32	54	Teriparatide 20 µg/day s.c.
4 years prior	132.00	1.00	364	105	After 12 months of teriparatide
3 years prior	10.07	0.12	15.37	35	After 24 months of teriparatide → switch to alendronate p.o. 5600/week for 2 years ***
1 year prior	10.22	0.13	19.41	30	Zoledronic acid 5 mg i.v.
current admission	11.14	0.13	22.58	37	Denosumab s.c. 60 mg every 6 months

Abbreviations: i.v.=intravenous; p.o.=oral; s.c.=subcutaneous; *** these 2 years of alendronate overlapped to the first 2 years of COVID-19 pandemic; the blue box represents 24-month teriparatide protocol; markers in blue represent the values under anabolic medication; suppressed markers in red represent the effect of bisphosphonates; N=normal

Figure 1. Whole body bone scintigraphy with ^{99m}Tc-HDP (20 mCi/740 MBq) on a 69-year-old female with a prior history of osteoporosis: vertebral uptake consistent with a previously identified incidental fragility fracture; also, mild uptake of the tracer at the level of the joints was consistent with chronic degenerative anomalies; severe dextro-concave scoliosis was described (on the right: anterior capture; on the left: posterior capture)



2. Discussions

Real-life-medicine poses multiple issues that require an individual decision while respecting the standard protocols. That is why a generalized decision is rather impractical. Here we introduce the clinical case of a lady in her late 60s with a known 6-year history of osteoporosis that required several difficult decisions along surveillance: at first, zoledronic acid represented an available solution, yet after one year, BMD decreased and adjustment was done by initiating a second sequence according to the teriparatide protocol. DXA-BMD, as well as the spectrum of bone turnover markers, qualified the patient as responsive and she further continued with oral bisphosphonates while being monitored *via* telemedicine amid COVID-19 pandemic. After 24 more months, a second decision of zoledronic acid was done, despite prior partial response, but digestive complains restricted the oral administration of anti-osteoporotic drugs. After one more year, denosumab was initiated and consecutive follow-up is essential. At this point, another challenging aspect was revealed: the discordance between DXA – based scores increase and the presence of an incidental fracture. A supplementary investigation was considered useful (Tc- whole body scintigraphy) noting the clinical presentation with local pain, dysfunctionality, and mild weight loss that also required rehabilitation management. Overall, severe osteoporosis and associated clinical elements might mimic a malignancy or a consumptive syndrome.

We further delve into particular insights of this vignette:

a. Discordant results between DXA-BMD improvement and incidental fractures

Despite having a good DXA-BMD response under specific therapy against osteoporosis, the presence of a complication such as a new vertebral fracture establishes a rather poor response to the treatment (a part from the fractures that are registered very early upon one drug initiation, thus the patient can hardly be considered as being non-responsive, and thus switching to another drug is not imperative) [12-14].

Lack of response to anti-osteoporotic drugs usually follows three main scenarios. One is represented by the lack of adherence to the actual treatment which is not the case of intravenous administration such as zoledronic acid or ibandronic acid that requires medical surveillance (as opposite to the self-administration of oral bisphosphonates or daily subcutaneous injections according to the teriparatide protocol) [15-17]; non-compliance being traditionally named “the Achilles’ heel of anti-fracture efficacy” [18]. The second explanation is related to the presence of a secondary cause of osteoporosis such as primary hyperparathyroidism, hyperthyroidism, Cushing’s syndrome, type 2 diabetes mellitus or even neurological diseases such as multiple sclerosis [19-24] that were excluded in this particular case. Also, a differential diagnosis with pathological fractures related to bone metastases is essential [25-27]. In this particular instance, screening protocols for cancer according to one individual sex and age are required, as well as additional imaging investigations such computed tomography, magnetic resonance imaging or even whole body bone scan (as we performed in this lady case) [28,29]. Another potential pitfall is represented by uncorrected vitamin D deficiency [30-33] (which was not found here). Despite controversies related to the specific anti-fracture intervention of single vitamin D supplementation, this represents a key element to be associated with anti-osteoporotic drugs (single or in addition to calcium supplements) [34-37]. Our patient continued her replacements including during pandemic years thus this issues was not applicable.

b. New fractures under anti-osteoporotic drugs

Once a patient, particularly a menopausal woman, is confirmed with osteoporosis, a higher risk of new spontaneous/low-trauma fractures is expected when compare to the general (non-osteoporotic) population (as reflected by the central DXA – based T-score,

despite specific therapy that is meant to reduce the fracture risk [38-40]. The current panel of available options (bisphosphonates, denosumab and teriparatide), also, includes romosozumab which is not available yet in our country [41-43]. This is a novel monoclonal antibody targeting sclerostin pathway that is recommended for one year followed by anti-resorptives in osteoporotic patients without increased cardiovascular risk [44-46].

c. Zoledronic acid as part of the osteoporosis management

As mentioned, we offered the patient twice this drug across the six years since first diagnosis. Generally, the medicine was proved to associate an increased anti-fracture efficacy upon annual administration, an effect that is prolonged up to 3 years after single 5 mg injection [47,48]. Moreover, after a 5-year exposure with annual administration, a drug holiday may be taken into consideration which, unfortunately, was not the case here [49-51]. Particular anti-proliferative effects have been pointed out in cancer survivors in both doses administered for bone metastasis and even osteoporosis [52-54]. In this instance, the good DXA-BMD profile that was registered under zoledronic acid was appreciated as insufficient due to a novel fracture thus a switch of therapy was decided.

d. Placing teriparatide as part of sequential therapy against osteoporosis

The patient on point was treated with this osteoanabolic drug and found to be responsive and compliant during the 2-year protocol. As showed in Table 2, the bone turnover markers presented a significant increase after the first year which is suggestive for the anabolic window [55-57]. Notably, the drug is also useful, not only in menopausal osteoporosis, but, also, on adult males diagnosed with idiopathic or glucocorticoid osteoporosis [58,59]. Non-vertebral, but, mostly, vertebral fracture risk is reduced under this bone forming agent that it should be continued with bisphosphonates or denosumab [60-62] (here, the decision of alendronate was taken through a digital consultation). Moreover, denosumab should be continued after one year with the same drug or a switch to bisphosphonate is necessary, not a drug holiday [63-66].

e. Treating osteoporotic patients during COVID-19 pandemic

In this case, the management of osteoporosis was essentially conducted in accordance with the pandemic regulations at that point; and a DXA scan was re-done after 2 years. A great amount of information has been published with respect to the coronavirus infection and associated changes of the medical and social systems, nevertheless, of individuals previously diagnosed with chronic conditions such as osteoporosis in addition to newly described virus-induced entities [67-70]. The main mechanisms of potential skeleton impairment were associated to low sun - related vitamin D exposure, lack of access to necessary check-ups, reduced physical activity (movement/exercise represents a booster or bone formation), deficiencies of medication adherence/disruption of prior regimes, changes of daily habits including adequate nutrients, an aggravation of sarcopenia and frailty with increased risk of fall [71-74]. The viral infection itself, particularly, severe forms with respiratory failure that required prolonged hospitalization were, also, detrimental to bone health, especially in previously diagnosed patients with bone loss [75-77].

f. Particular aspects of investigations amidst osteoporosis

The mentioned case introduced the profile of bone turnover markers that was highly suggestive for the associated therapy: increased values upon the first 1-year teriparatide regime and suppressed under anti-resorptives. Despite high inter- and intra- individual variations, and despite not being useful at osteoporosis diagnosis, these biomolecules are very useful in order to follow-up the response to anti-fracture drugs [78-80]. As prior specified, the expected low values were found upon the second round of zoledronate, yet, the fracture profile was not consistent with this good response and a certain discordance

between the exact markers values and an incidental fracture might be expected in this particular matter [81-83]. Nevertheless, further periodic assays of these biochemical parameters are planned for our case (mostly at the moment at DXA re-examination after at least 12 months since starting denosumab).

Of note, as shown in Table 1, our patient had unexpected low BMD (and associated T-score) at the level of third distal radius of the non-dominant forearm. Generally, this region is scanned in primary hyperparathyroidism (which was ruled out in this case), but, also, in traditional cases with primary osteoporosis if the patient associates non-interpretable data at central DXA, namely at lumbar spine (for instance, due to severe spine deformities or following vertebral fractures surgery) and/or at hip region (for example, due to coxarthrosis or hip replacements) [84-86]. Alternatively, other investigations might help to assess the bone fragility, such as high resolution peripheral quantitative computed tomography or magnetic resonance imaging, while lumbar DXA – derivate trabecular bone score (TBS) might identify damage of bone microarchitecture [87-89]. In this case, TBS value following the 2-year weekly alendronate regime was of 1,308, and of 1,293, respectively, after the most recent round of zoledronate.

A decision of performing a whole body bone scintigram in dealing with complicated osteoporosis should be taken into consideration (if available). While this type of skeletal assessment is less frequently used nowadays, a cost-benefit analysis might favor it in a selected subgroup of patients [90].

g. Hypo-anabolic syndrome/weight loss in osteoporosis: is this a red flag?

At first, weight loss in a patient under anti-fracture medication might suggest concomitant digestive conditions, including malabsorption or negative side effects of oral drugs, but, also, concomitant disorders with high metabolic rates such as excess of thyroid hormones or cancers [91]. However, an associated component of depression or even eating behavior anomalies should be ruled out, particularly, in subjects with chronic pain and disability due to long standing, complicated osteoporosis and/or osteoarthritis [92,93]. On the other hand, some anti-depressants are cited to reduce BMD [94], while, generally, excessive weight loss is a contributor to bone damage since across life span the achievement of peak bone mass to elderly [95,96].

h. From fractures – associated pain to non-pharmacologic approach of osteoporosis

As expected, a local pain is consistent to some vertebral fractures (but overall one third of them may be completely asymptomatic) and a prompt intervention is required. On the other hand, pain might be a useful clue to bring one patient to a medical check-up, while clinically silent fractures might delay the diagnosis [97,98]. Pain management is necessary under these circumstances, while specific rehabilitation programs depend of the fracture site [99,100]. Musculoskeletal exercises are recommended based on the comorbidities, patient' age and affected skeleton areas in addition to maintaining an active lifestyle and healthy nutritional habits [101-104].

3. Materials and Methods

We aim was to present a case of severe osteoporosis with concern to an adult female who was under specific medication against the condition while she experienced inexplicable weight loss in association with an incidental fracture inconsistent with DXA changes. Challenges of the case management and decision making are further on explained.

The data are provided after the signed informed consent by the patient on point was available. We introduced the medical records that are focused on the management of osteoporosis and the rehabilitation plan. DXA (Dual-Energy X-Ray Absorptiometry) was performed with a GE Lunar Prodigy device.

Case report

a. Admission

A 69-year-old, heavy smoker (since the last 20 years) woman coming from non-endemic area was admitted for the evaluation of her previous osteoporosis diagnosis while she experienced recent weight loss (5 kg amid latest months) associated with intermittent back pain and reduced physical mobility and an overall clinical deterioration without an apparent cause. On admission, a low body mass index of 18.5 kg/sqm was identified and a depressive mood.

b. Medical history

The family medical history was irrelevant (neither one of her parents suffered from osteoporosis, nor fragility fractures), while her personal medical data included treatment for high blood pressure during the last decade, a mild hypercholesterolemia, and a small goiter with normal thyroid function. The subject was also known with a long history of treated osteoporosis in relationship with her age and menopausal status (she entered physiological menopause at 47 years), noting a single traditional risk factor for osteoporosis, namely smoking (her prior body mass index was within normal values).

She was first found with osteoporosis 6 years ago and a single annual injection with zoledronic acid 5 mg was offered to her as first line anti-osteoporotic therapy in association with daily cholecalciferol initially 2000 IU for 3 months followed by 1000 IU/day. After 12 months, she registered a bone mineral density (BMD) loss (a lowering T-score from -3.6 SD to -4.1 SD at lumbar site) without the identification of a secondary cause and the confirmation of adequate levels of 25-hydroxyvitamin D, thus teriparatide (subcutaneous 20 µg/day) was initiated and continued for 2 years according to the national protocol [10,11]. At the end of this time frame, an adequate response was appreciated under the bone anabolic drug by switching from lumbar T-score of -4.1 to -3.5 without new fractures (she experienced transitory hypercalcemia within the months 22-24 of teriparatide).

Further on, she continued with oral bisphosphonates for 2 years (that represented the first two years of COVID-19 pandemic and she did not perform any DXA exam in the meantime). After lockdown restrictions allowed a hospital evaluation (in order to have the DXA exam done at the same machine), the lady performed a new DXA scan; she was found with a lumbar T-score of -3.9 SD. Once again, a decision of zoledronic acid was taken as part of the sequence management due to mild gastric accuses that restricted oral bisphosphonates.

After one more year, an increase of T-score to -2.9 SD was registered at L1-4 level (which represented the highest T-score we ever identified in this patient regardless the timing of evaluation). **(Table 1)**

Moreover, the blood bone turnover markers such as osteocalcin (bone formation marker) and CrossLaps (bone resorption marker) remained suppressed as a traditional (expected) response under bisphosphonates. **(Table 2)**

However, an incidental fracture was detected at the level of thoracic T7 vertebra according to screening X-Ray scan. At this point she experienced back pain, depressive mood, reduced appetite and weight loss. The traditional screening for cancers according to her age was done and found negative. No endocrine cause such as hyperthyroidism or adrenal failure was identified, while the blood biochemistry assays were normal, as well as the hormonal panel, including 25-hydroxyvitamin D (25OHD) of 30.2 ng/mL (normal levels between 20 and 100 ng/mL) and parathormone (PTH) of 45.01 pg/mL (normal values between 15 and 65 pg/mL).

Under these circumstances, an additional exploration was decided based on a multidisciplinary approach and the female subject underwent a whole body bone scintigraphy with ^{99m}Tc-Technetium (Tc)-HDP (20 mCi/740 MBq). Late (2-hour post-injection) uptake was suggestive for the vertebral fracture that was already pinpointed by X-Ray examination. **(Figure 1)**

A decision of switching to denosumab (60 mg every 6 months) was taken in association with following vitamin D supplementation (cholecalciferol 1000 IU/day). A DXA re-scan was planned after one year. A rehabilitation program was also started. The main

rehabilitation objectives were: relieving pain, improving paravertebral, gluteal and abdominal muscle tone and strength, walking training. The patient received non-steroidal anti-inflammatory drugs for pain, as well, as needed, and she was further referred for initiating an anti-depressive medication. Long term follow-up is recommended.

4. Conclusion

Osteoporosis represents a long standing condition that requires a long term plan of surveillance and intervention; real-life medicine associates multiple issues that require a continuous adjustment of individual decision and a personalized approach from a multidisciplinary perspective, for a successful functional rehabilitation and to improve the quality of life.

Abbreviations

BMD	bone mineral density
25OHD	25-hydroxyvitamin D
DXA	Dual-Energy X-Ray Absorptiometry
PTH	parathyroid hormone (parathormone)
Tc	Technetium
TBS	trabecular bone score
IU	international units

Supplementary Materials: Not applicable

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