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BONE MINERAL DENSITY, FRAGILITY FRACTURES AND CLINICAL RISK FACTORS

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ABSTRACT

Osteoporosis affects the skeletal system and is characterized by a reduction in bone strength that predisposes one to an increased risk of fractures. In Italy, about 3.5 million women and 1 million men suffers from osteoporosis. These numbers are set to increase in the coming twenty years because the percentage of the Italian population over 65 will increase by 25%.
The purpose of this study is to evaluate the general characteristics of a population of patients suffering from osteoporosis and the relation with comorbidity.
A single site, open-label, investigator-initiated, retrospective trial was conducted at the Bone Metabolic Disease Clinic, Department of Physical Medicine and Rehabilitation, University Hospital "P. Giaccone", Palermo (Italy). 1500 patients of Bone Metabolic Diseases Clinic were enrolled from January 2009 and September 2017.
All the patients were evaluated by Hologic Discovery QDR and subjected to a questionnaire that investigated general characteristics, life style, clinical data, osteoporosis pharmacological treatment, completed physical therapy, and Bone Densitometry results.
The subjects with increased fracture risk have a high mean age, a lower BMI, report practicing less physical activity and less sun exposure. They also have a higher CIRS-comorbidity index and report previous fragility fractures more often. The study demonstrated a statistically significant association between the risk of fragility fractures, T-Score ≤-1, and comorbidity.
This study could contribute to develop a protocol for primary prevention of fragility fractures in the female population affected by osteoporosis demonstrating a correlation between comorbidity and fragility fractures incidences.

1. Introduction

Osteoporosis is a systemic skeletal disease, characterized by low bone density and deterioration of bone architecture, that causes weakening of the bones which increases the chances of fracture[1][2].
Approximately 10 million men and women in the U.S. have osteoporosis. Osteoporosis-related fractures can increase pain, disability, nursing home placement, total health care costs and mortality. [3][4]
International data demonstrate that osteoporosis fractures of the proximal femur occur in 18% of women and in 6% of men. This type of fracture represents 83% of the causes of hospitalization in osteoporotic patients. Within one year from the fracture, patients with fractured proximal femur present a mortality rate of 15-30%. [5][6]
Vertebral fractures are the most common osteoporosis complications.

According to data reported by the EPOS study group in 2012, in Europe one in three women over 65 have spinal deformities [4] (European Prospective Osteoporosis Studies (EPOS) Group, 2002) [7]. Vertebral fractures cause a strong negative effect on the quality of life and an increase in mortality (10 times greater than the subjects that have never had a fracture) – [8]
Colles' fractures are most frequent in women between 40 and 50 years of age with osteoporosis and in men under 70 years old. It has been demonstrated that this type of fracture increases the risk of a new wrist fracture up to three times, almost two times that of femur and vertebral fractures and two and half times that of fractures in other locations. [9]
Osteoporosis fractures that take place in another location ("Minor fractures") belong to the foot/ankle or the ribs and double the risk of femur, vertebral and wrist fractures. [8]

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The gold standard for the diagnosis of osteoporosis is represented by bone mineral density (BMD) using non-invasive dual-energy x-ray absorptiometry. This exam has an important role in the evaluation of individuals at risk of osteoporosis, and in helping clinicians advise patients about the appropriate use of antifracture treatment. Compared with alternative bone densitometry techniques, DXA examinations have a number of advantages that include a consensus that BMD results can be interpreted using the World Health Organization T-score definition of osteoporosis, a proven ability to predict fracture risk, proven effectiveness at targeting antifracture therapies, and the ability to monitor response to treatment. [10]

It has been observed that the risk of fracture begins to rise exponentially for densitometric values of T-score < -2.5 SD which, according to OMS, represents a threshold for the diagnostic of osteoporosis.

The risk of fracture is determined by a combination of factors that predominately work through a reduction of BMD and by other factors which are partially or totally independent from the latter one (characteristics of bone tissue that can not be assessed by BMD and extra-osseous factors).

The distinction is certainly not that rigid and a lot of them act with multiple mechanisms at the same time. Along with the factors associated independently with the risk of osteoporosis and fractures - age, previous fragility fractures and falls must also be counted. Furthermore, contaminating diseases emphasise the risk of fracture. By virtue of these considerations, it is clear that the concurrency of more factors increases the risk of fragility fractures [11] [12]. Therefore, the valuation of BMD is appropriate for the diagnosis of osteoporosis (diagnostic threshold) but not to identify and, hence, treat the subjects pharmacologically at high risk of fracture (therapeutic threshold).

The drug therapy takes advantage of the use of bisphosphonates, receptor activator of nuclear factor kappa-B ligand inhibitors, estrogen agonists/antagonists, parathyroid hormone analogues, and calcitonin [13].

The purpose of the study is individuated by the general characteristics of a patient population which stratify the risk of fragility fracture and indicate a correlation between T-score and comorbidity through an algorithm.

Such data will enable us to precociously identify individuals at risk so as to practice effective prevention first and reduce fracture events.

2. Material and methods

Design and eligibility criteria

This single site, open-label, investigator-initiated, retrospective study was conducted between January 2009 and September 2017 with a total enrollment of 1500 patients. All patients are spontaneously affirmed at the Bone Metabolic Diseases Clinic of Department of Physical Medicine and Rehabilitation of University Hospital "P. Giaccone" of Palermo. The study was conducted in accordance with the 1964 Helsinki declaration and subsequent amendments and the principles of Good Practice. To all the patients, the clinical investigator had explained the nature and the aim of the study and was asked to give written consent to the collection of data contained in their medical records.

Inclusion criteria: subject >18 years that provide signed informal consent.

Subjects with either of the following conditions were not entitled to enter the study: cognitive impairment and allurement.

Evaluation tests

All the subjects were evaluated by the Hologic Discovery QDR and subjected to a questionnaire that investigated:

- General characteristics (sex; age; menarche age; menopause age; weight and height, measured by the physician);
- Lifestyle (cigarette smoking habits, cigarettes/day of current smokers; consumption of milk and/or milk products (number of times/week); practice of physical activity (for example, Pilates, postural gymnastics, dancing, aerobic activities, swimming, performed at least twice a week); sun exposure at least thirty minutes daily for a minimum of three-four months per year;
- Clinical data (comorbidity index CIRS (Parmalee PA et al, 1995); use of corticosteroids (dose > 5 mg/die for a period exceeding three months); self-reported family history of osteoporosis and previous fragility fracture);
- Osteoporosis pharmacological treatment (previously prescribed and already taken by the patient or prescribed during the evaluation);
- Physical therapy/functional rehabilitation carried out;
- Date of US Bone Densitometry execution and result.

Statistical analysis

The data are expressed as means ± standard deviation (SD) or median (quartile 1 – Q1; quartile 3 – Q3) for quantitative measures, and frequency percentages for all discrete variables. The study population was stratified in two groups, considering the fracture risk from the T-Score (BIBLIO HOLOGIC):

1. T-score <-1.0 SD, "low bone mass, increased risk for fracture";
2. T-score ≥-1.0 SD.

The differential distribution of the subjects' characteristics was analyzed using the chi-square test or the Fisher's Exact test for categorical variables. Quantitative variables were comparable using the GLM procedure, after testing for homoscedasticity (Levene's test; the Welch's ANOVA was taken into consideration in case of heteroscedasticity), for variables with normal distribution verified by the Shapiro-Wilk test. The Wilcoxon test Rank-Sum was reckoned for variables not normally distributed.

A logistic regression model with outcome T-score (<-1.0 SD "low bone mass, increased risk for fracture" vs T-score ≥-1.0 SD) was defined. The independent variables referred to in the multivariable model were identified among those associated at the unvaried level with $p<0.20$, using a stepwise selection of predictors, with significance to enter 0.15 and significance to stay 0.20. Odds ratio (OR) and 95% Confidence Intervals (CI) for identified variables is to be submitted. A further logistic regression model has been set out to identify the characteristics associated with previous fragility fractures. Statistical significance was declared per $p<0.05$. The analyses were carried out using SAS statistical software 9.3.

3. Results

The study population included n=1500 subjects. 94% of the population consists of women, the mean age of the participants is 63.7±10.1 years. The mean Body Mass Index (BMI) is 27.3±4.6 kg/m2; only 1 % of the population has a BMI<18.5 kg/m2 and is underweight, while 68.5% of subjects evaluated is overweight or obese (BMI≥25 kg/m2). The mean for

CIRS - Comorbidity Index, i.e. the number of pathologies with gravity greater than or equal to "moderate" (excluding psychiatric/behavioral pathologies), is 2.3±1.6.

During the evaluation study visit, 468 subjects (31.2%) reported to already be taking at least one drug for the osteoporosis. Among 1,032 patients that had never taken osteoporosis medicine, drugs for osteoporosis were prescribed to 394 subjects for the first time. The osteoporosis drugs prescribed before the evaluation are: Integrators (calcium, cholecalciferol, calcitriol, vitamin kappa) for 71.4% of subjects, anti-absorptive drugs for 50%, anabolic drugs for 6.6%. Instead, the drugs for osteoporosis treatment prescribed during the evaluation are integrators for 77.7% of subjects, anti-absorptive drugs for 33.4%, and anabolic drugs for 5.7% of subjects (Figures 1 and 2).

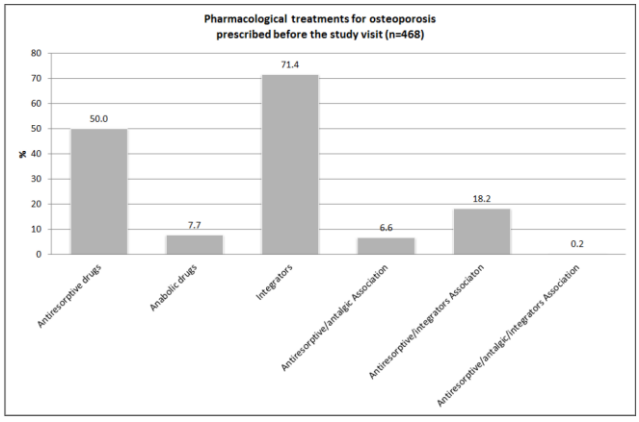

Figure 1 - Pharmacological treatments for osteoporosis prescribed before the study visit. (*Antiresorptive drugs:* alendronic A.; clodronic A.; ibandronic A.; risedronic A.; Ibandronate sodium; strontium ranelate; Risedronate sodium; *Anabolic drugs:* calcitonin; parathormone; teriparatide; *Integrators:* calcium; calcium carbonate; calcium carbonate/colecalciferol; Calcitriol; cholecalciferol; Vit. kappa; *Antiresorptive/antalgic Association:* clodronic A./lidocaine; *Antiresorptive/integrators associaton:* alendronic A./colecalciferol; clodrinic A./calcium carbonate/colecalciferol; risedronate sodium/calcium carbonate/colecalciferol; ranelate strontium/calcium carbonate/colecalciferol; ranelate strontium/colecalciferol; *Antiresorptive/antalgic/integrators association:* clodronic A./lidocaine/calcium; clodronic A./lidocaine/colecalciferol.)

Among the subjects that already had a prescription for osteoporosis drugs before the evaluation, the most frequently re-confirmed therapies were those for integrators, followed by anti-absorptive drugs (confirmed in 87.5% and in 80.9% of cases, respectively).

The subjects that have an increased fracture risk based on the T-score (T-score <-1.0 DS) number 1,011 (67.4% of the population). Table 1 presents the differential distribution of the subjects' characteristics with an increased fracture risk. Compared to people who do not have an increased fracture risk based on the results of T-score, subjects with increased fracture risk have a high mean age, a lower BMI, report to practice less physical activity and less sun exposure.

They also have a higher CIRS-comorbidity index and report more often previous fragility fractures.

Family history of osteoporosis and consumption of milk and/or milk products were not significantly associated with increased fracture risk. The corticosteroids use in a dose > 5 mg/die for a period exceeding three months has a borderline association with the increased fracture risk.

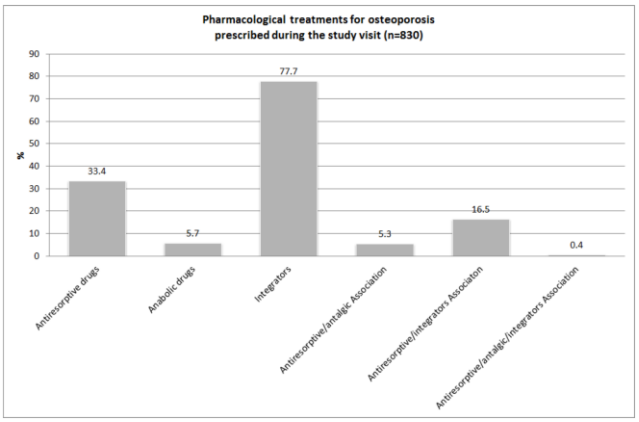

Figure 2 - Pharmacological treatments for osteoporosis prescribed during the study visit.

	T-score ≥-1 (n=489, 32.6%)	T-score < -1.0 *Low bone mass, increased risk for fracture* (n=1011, 67.4%)	P-Value
Female gender, n (%)	450 (92.0)	960 (95.0)	**0.0251**
Age, years, mean±SD	61.1±9.8	65.0±10.0	**<0.0001**
Age at menarche, years, mean±SD	12.1±1.5	12.3±1.5	**0.0126**
Age at menopause, years, mean±SD	47.9±5.0	47.5±5.2	0.1312
Weight kg, mean±SD	69.8±12.8	67.6±12.0	**0.0029**
Height cm, mean±SD	159.0±5.7	158.0±6.6	0.0021
BMI, kg/m^2, mean±SD	27.6±4.8	27.1±4.5	**0.0381**
Classes of BMI, n (%) Underweight (BMI<18.5 kg/m^2) Normal weight (18.5 kg/m^2≤BMI<25 kg/m^2) Overweight (25 kg/m^2≤BMI<30 kg/m^2) Obesity (BMI ≥ 30 kg/m^2)	 7 (1.4) 134 (27.4) 215 (44.0) 133 (27.2)	 8 (0.8) 324 (32.1) 452 (44.7) 227 (22.5)	0.0781
Smoking habit, n (%)	192 (39.3)	323 (32.0)	**0.0052**
If actual smoker, cig/day, mean±SD	13.0±7.0	14.2±8.1	0.2494
Consumption of milk and/or milk products, n (%) never 1-2 days per week 3 or more days a week	 88 (18.0) 70 (14.3) 331 (67.7)	 204 (20.2) 128 (12.7) 679 (67.2)	0.4716
Physical activity practice, n (%)	81 (16.6)	125 (12.4)	**0.0267**
Sun exposure, n (%)	238 (48.7)	392 (38.8)	**0.0003**
CIRS-Comorbidity Index, mean±SD	1.8±1.4	2.6±1.7	**<0.0001**
Osteoporosis family history, n (%)	127 (26.0)	245 (24.2)	0.4650
Corticosteroids use 3+ months, n (%)	55 (11.3)	151 (14.9)	0.0517
Previous fragility fractures, n (%)	64 (13.1)	277 (27.4)	**<0.0001**
Physical therapy, n (%)	97 (19.8)	300 (29.7)	**<0.0001**
Functional Rehabilitation, n (%)	104 (21.3)	319 (31.6)	**<0.0001**

Table 1 - Stratification of the fracture risk based on T-score - Hologic Discovery QDR

Table 2 shows the characteristics associated with an increased fracture risk based on T-score. The logistic regression model was defined considering only female patients, considering the small sample size of the male group. In the multivariable model, age is associated with a significant increase in fracture risk, as well as a weight ≤ 75 kg, previous fragility fractures and CIRS comorbidity index ≥ 3.

Table 3 presents the characteristics associated with previous fragility fractures in a multivariable model; this model has been defined considering only female patients. Age, smoking, CIRS comorbidity index ≥ 3 , and QUS T-Score <-1 DS are associated with previous fragility fractures. The subjects that practice regular physical activity have a lower probability of having had previous fragility fractures. The consumption of milk and/or milk products more than 3 times/week is also associated with the probability of previous fragility fractures.

	OR	95% CI	p-value
Age (years)	1.03	1.01-1.04	<0.0001
Weight ≤75 kg	1.36	1.03-1.79	0.0311
Previous fragility fractures	1.78	1.27-2.49	0.0007
CIRS_C≥3	2.17	1.66-2.83	<0.0001
Regular sun exposure	0.83	0.65-1.06	0.1366
Corticosteroids for more than 3 months	1.47	0.99-2.19	0.0545
Actual smoker	1.00	0.77-1.30	0.9820
Physical activity practice	1.04	0.74-1.46	0.8333
Consumption of milk and/or milk product (3+ times per week)	1.01	0.87-1.17	0.9390

Table 2 - Characteristics associated with "*low bone mass, increased risk for fracture*" (T<-1.0) (only in women)

	OR	95% CI	P-Value
Age (years)	1.07	1.05-1.09	<0.0001
Weight ≤75 kg	1.03	0.74-1.44	0.8431
CIRS_C≥3	2.31	1.75-3.06	<0.0001
Regular sun exposure	0.85	0.63-1.14	0.2828
Corticosteroids for more than 3 months	1.42	0.97-2.08	0.0679
Actual smoker	1.42	1.03-1.98	0.0349
Physical activity practice	0.57	0.34-0.97	0.0375
Consumption of milk and/or milk products (3+ times per week)	0.85	0.72-0.99	0.0478
T-score<-1	1.79	1.28-2.50	0.0007

Table 3 - Characteristics associated with previous fragility fractures (only in women)

4. Discussion

The retrospective study demonstrated a statistically significant association between the risk of fragility fractures, T-Score ≤-1, and comorbidity. [13] Furthermore, T-score ≤-1.0 coincides with the presence of previous fragility fractures and weight less than 75kg. The date, in our significant option, is the relation between T-score ≤-1 and CIRS co-morbidity index ≥3. The identification of this cut off (CIRS ≥3) could be added to the criteria for the implementation of primary prevention in osteoporosis [14] [15].

Primary and secondary prevention of fragility fractures

Primary prevention should already start at a young age in order to reach an appropriate mass peak through physical activity, diet and the abolition of modifiable risk factors (ex. cigarette smoking). It should then continue into adulthood by identifying those at risk. Equally important is secondary prevention with the administration of calcium, vitamin D, bisphosphonates, monoclonal antibodies and anti-irritants associated with rehabilitative treatment and finally the tertiary one, limiting the risk of falls for the prevention of new fractures. [16]

The elimination of modifiable risk factors should therefore be recommended to all, while the use of osteoporosis drugs should be conditioned by the evaluation of the risk / benefit ratio. After all, the WHO establishes a diagnostic threshold based on the T-Score values (presence of osteoporosis for T-Score ≤-2.5), but it does not identify it as the only parameter for the prescription of drug treatment. In fact, the risk of fracture expressed only by the densitometric data ignores other important factors that, as we have seen before, contribute to determine the fracture risk, that is the "clinical risk factors". [17]

For this purpose, different “computers” as the DeFra and the FRAX (the most used) [18] have been established. The former calculates the individual risk profile of a fracture integrating clinical risk factors with bone density values (BMD), while the latter identifies it at ten years through the anamnestic research of risk factors of bone fragility and falls [19] [20]. The quantification of this risk provides an "instantaneous" datum, which must be re-estimated in terms of “life-time long risk” or, more conveniently, in “10 years’ fracture risk”.

Limitations of the study

It is important to define the strengths and limits of our study. Firstly, the large sample size is an important strength as much as the numerous variables included that evaluate the modifiable and not- modifiable osteoporosis risk factors. The inclusion of densitometry within the diagnostic exams and the use of the same Hologic Discovery QDR for all the patients enrolled has to be considered an important strength.

The principal limitation of the study is that T-Score index could be associated with the evaluation of dorso-lumbar radiography with Genant's visual semiquantitative assessment for a more precise analysis of vertebral fractures.

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