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### ► To cite this version:

Rachel Litke, Francois Puisieux, Julien Paccou, Jean-Baptiste Beuscart, Isabelle Delabriere. Étude rétrospective évaluant l'exploration étiologique de l'ostéoporose chez les hommes âgés dans un service de gériatrie français. *Annales d'Endocrinologie = Annals of Endocrinology*, 2022, *Annales d'Endocrinologie*, 10.1016/j.ando.2022.01.002 . hal-04554753

**HAL Id: hal-04554753**

<https://hal.univ-lille.fr/hal-04554753v1>

Submitted on 22 Jul 2024

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## Title page

### **A retrospective study on the etiological exploration of osteoporosis in aging men in a French geriatric setting**

### **Etude rétrospective évaluant l'exploration étiologique de l'ostéoporose chez les hommes âgés dans un service de gériatrie français**

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Word count: 2808 words, 18917 characters including spaces

**ABSTRACT** (Introduction, Objective, Methods, Results, Discussion)

**Introduction** Osteoporosis in older men is common and causes significant mortality and morbidity. Some data suggest that conditions leading to bone fragility, including osteoporosis, are under-identified and undertreated in men. Additionally, 50% of the causes of osteoporosis are secondary in men. The latest Endocrine Society and different Rheumatology Societies Guidelines recommend additional laboratory investigations in men with osteoporosis so as to treat them more efficiently.

**Main Goal of the Study** Our aim was to determine whether men managed in our geriatrics center, diagnosed with osteoporosis, underwent investigations to determine the aetiology of osteoporosis and other bone fragility conditions and what the secondary causes were.

**Materials and Method** We conducted a monocentric, retrospective study including all men seen at the geriatric consult in 2016 diagnosed with osteoporosis. For each patient, we evaluated our clinical practice, whether common secondary causes were sought-after and what these aetiologies were.

**Results** Among the 121 men with a diagnosis of osteoporosis seen at the geriatric consult at the Lille University Hospital in 2016, only 51 had undergone further investigations. Among the 3 major secondary causes were identified: 17,6% glucocorticoid induced, 13,7% treatment induced hypogonadism, 11,7% late onset hypogonadism.

**Conclusions** A more efficient etiological assessment of osteoporosis in older men could be achieved and would improve management for our patients. This can be achieved by a better knowledge of the recommendations for etiological assessment of bone fragility and osteoporosis and a dedicated consultation within the geriatric sector.

## Résumé français

**Introduction** L'ostéoporose de l'homme âgé est une pathologie fréquente, et à l'origine d'une morbi-mortalité importante. Des données suggèrent que la fragilité osseuse, et l'ostéoporose en particulier, sont sous-diagnostiquées et insuffisamment prises en charge chez l'homme, alors que, pour ce sexe, 50% des ostéoporoses ont une cause secondaire. C'est dans ce contexte qu'en 2012, l'Endocrine Society a émis des recommandations proposant des explorations biologiques complémentaires pour les hommes ostéoporotiques afin d'améliorer la prise en charge. Les sociétés savantes de rhumatologie émettent des recommandations comparables, les plus récentes sont les recommandations françaises de 2021.

**Objectif principal** L'objectif principal de ce travail était de déterminer si les patients ostéoporotiques pris en charge en consultation gériatrique au CHRU de Lille (toutes consultations de spécialité confondues) bénéficiaient d'explorations à visée étiologique. Nos objectifs secondaires étaient d'identifier les différentes étiologies de fragilité osseuse repérées chez ces patients et d'évaluer s'il y avait des variables influençant la réalisation ou non d'explorations étiologiques de la fragilité osseuse.

**Matériels et Méthode** Nous avons réalisé une étude observationnelle, rétrospective, monocentrique, incluant tous les hommes ostéoporotiques pris en charge à la consultation gériatrique du CHRU de Lille en 2016 (du 1er janvier 2016 au 31 décembre 2016). Pour chaque patient, nous avons évalué nos pratiques cliniques, déterminé si des explorations à visée étiologique avaient été réalisées et quelles étaient les étiologies identifiées.

**Résultats** Parmi les 121 hommes ostéoporotiques venus en consultation gériatrique au CHRU de Lille en 2016, 51 ont eu un bilan à visée étiologique. Les 3 étiologies principales identifiées chez ces patients étaient: une ostéoporose cortico-induite dans 17,6% des cas, un hypogonadisme iatrogène dans 13,7% des cas, un déficit en androgènes lié à l'âge (DALA) dans 11,7 % des cas.

**Conclusion** Les investigations étiologiques réalisées chez nos patients ostéoporotiques sont insuffisantes alors que les recommandations des sociétés savantes de rhumatologie et d'endocrinologie fournissent un cadre précis pour le diagnostic et la prise en charge de l'ostéoporose masculine. Nous pourrions peut-être améliorer le taux de réalisations

d'explorations à visée étiologique de la fragilité osseuse chez les hommes âgés par une meilleure information des recommandations et le développement d'une consultation dédiée au sein des services de gériatrie. Nous améliorerons ainsi aussi l'efficacité thérapeutique du traitement de la fragilité osseuse et de l'ostéoporose chez l'homme.

Keywords: aging, geriatrics, osteoporosis, late onset hypogonadism

Mots clés: vieillissement, ostéoporose, déficit androgénique lié à l'âge

### **Highlights:**

- 1/ Osteoporosis in aging men is underdiagnosed and undertreated
- 2/ Etiological assessment of bone fragility in men improves clinical management outcomes
- 3/ Etiological assessment remains insufficient in older men with a diagnosis of osteoporosis
- 4/ It seems necessary to develop standardized/homogenized protocols for professionals
- 5/ Dedicated consults for osteoporosis can improve osteoporotic management in older men

### **1. Introduction**

Although long regarded as an essentially female disease, it is now recognized that osteoporosis also affects men with a prevalence reaching 16.6% after age 80 in a recent American study [1]. In 2000, one third of osteoporotic fractures around the world occurred in men [2]. In case of fracture, consequences seem more serious in men than in women: early excess mortality ensuing a femoral neck or trochanteric fracture is 3 times greater in men than in women in a 2007 study [3]. The same is true for the overall mortality rate after a fracture which is higher in men than in women [4].

Despite abundant epidemiological evidence of the seriousness of the phenomenon, osteoporosis remains under-diagnosed and under-treated in men, even in those who have had a fracture [5]. Although bisphosphonate therapy has been shown to reduce the risk of

mortality in frail men after the occurrence of a femoral fracture [6], these treatments are still less prescribed for men than for women [7].

Semiologically, male osteoporosis can be classified into two categories: (i) primary osteoporosis, most often without identified etiology, even if genetic, familial and environmental factors certainly play an important role; (ii) secondary osteoporosis defined as osteoporosis due to an underlying cause or iatrogenic origin. There is a secondary etiology to osteoporosis in 50% of men [8]. The most frequently diagnosed etiologies are: excessive alcohol consumption, hypercorticism (exogenous and endogenous), hypogonadism of iatrogenic origin (in prostate cancer most frequently) and late-onset hypogonadism (LOH), vitamin D deficiencies [9,10].

The diagnosis of secondary osteoporosis remains a challenge because the causes are numerous, sometimes rare or intricate and require specific diagnostic tests [11].

It is however essential to make the etiological diagnosis of osteoporosis, differentiating it from other bone fragility conditions, because it leads to better results in treatment management. Indeed, specific treatment of underlying conditions and conditions known to cause bone fragility such as hyperparathyroidism, hypogonadism or hyperthyroidism may increase bone density by 10-20% [12]. In order to help disease management, an increasing number of professional guidelines have been issued [13, 14] for the diagnosis and management of osteoporosis in men.

Aware that male osteoporosis is frequently under-diagnosed, we wished to evaluate whether men with osteoporosis who were referred to the geriatrics consult (which include falls, memory, nephrogeriatrics, oncogeriatrics, pain management, nutrition, and general geriatric evaluation consultations) at the Lille University Hospital during the year 2016, had etiological

explorations as defined by the professional guidelines. Our primary objective was to determine whether men with a chart diagnosis of osteoporosis underwent etiological explorations for osteoporosis and other bone fragility conditions. Our secondary objectives were to determine which were the secondary etiologies of osteoporosis and other causes of bone fragility identified in the patients in the study, and to assess whether there were variables influencing whether or not etiological explorations of bone fragility and osteoporosis were performed.

## **2. Methods**

### **2.1 Study design**

This is a retrospective, single-center study, including all men diagnosed with osteoporosis who consulted in geriatrics at the Lille University Hospital during the year 2016.

### **2.2 Study Population**

We included all men with a history of osteoporosis referred to the geriatric consult (which include consults for memory, for standardized geriatric assessment, for oncogeriatrics assessment, for nephrogeriatrics and falls assessment) of the geriatric clinic “Les Bateliers” of the Lille University hospital between January 1<sup>st</sup> and December 31<sup>st</sup>, 2016. For patients who consulted several times during 2016, data from all consultations were collected.

The patient census was conducted by the Department of Medical Informatics (DIM) with the diagnostic coding software of the Lille University Hospital (CORA). Due to the absence of ICD-10 coding in consultation, our query strategy was as follows: for all men managed during the year 2016 at the consultation, we searched for an 'osteoporosis' coding and / or a CCAM act ‘bone densitometry’ during a previous hospitalization at the Lille University Hospital. The different codes used for osteoporosis were: M80 \* (osteoporotic fracture); M81 \*

(osteoporosis without fracture); M821 \* (osteoporosis with endocrine disease). As the DIM codes are entered for billing purposes rather than research or care purposes, inclusion of patients without a diagnosis of osteoporosis but labeled as such for billing purposes could be possible. This is why we decided to have a 2-step check for the diagnosis of osteoporosis and included patients with a DIM code for osteoporosis and records of a bone mineral density measurement as described below (refer to the study flow chart).

For each patient included we verified the diagnostic elements for osteoporosis in the electronic health records. Criteria retained for the diagnosis of osteoporosis were those established by WHO (World Health Organization) in 1994 and revised in 2001 [18]. The diagnosis is based on the T-score measured by bone densitometry (BMD), also known as dual-energy X-ray absorptiometry. Bone mineral density measurement procedures were identified through appropriate procedure codes using the DIM referral database. Measurements at the University Hospital of Lille, include BMD of the femoral neck, the lumbar vertebrae and if these sites are not interpretable the lower 1/3 of the radius. This is in line with the criteria of the GRIO (Groupe de Recherche et d'Information sur les Ostéoporoses).

### **2.3 Etiological assessment**

The purpose of our study was to evaluate whether an etiological assessment had been conducted for the osteoporotic men managed in our geriatric clinic before, or during the year 2016 (and before December 31<sup>st</sup> 2016). The criteria we collected to attest that an etiological exploration had been performed were the first line evaluation tests recommended by the different professional guidelines for an etiological diagnosis of osteoporosis in men, namely: serum calcium, phosphate, creatinine (with estimated glomerular filtration rate), alkaline phosphatase, liver function, 25(OH)Vitamin D, total testosterone, complete blood count, and



24-h urinary calcium. If all these examinations were performed before December 31<sup>st</sup> 2016, we concluded that an etiological exploration had been conducted. We did not determine a minimum or maximum delay between the diagnosis of osteoporosis and the accomplishment of the etiological assessment as long as the assessment was conducted after or concurrently with the diagnosis of osteoporosis.

## **2.4 Data collection**

We used administrative databases and the electronic health records to obtain data on demographics, diagnoses, the conducted etiological explorations, drugs prescribed, and the measurement of bone mineral density. Any assessment which was not done at the University Hospital of Lille and/or for which the results were not included in the electronic health records could not be acknowledged in our study.

## **2.5 Ethics and approvals**

The data was entered into an Excel file in the form of binary or digital variables. The study was registered with the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés). In view of the study's design (retrospective study), no written informed consent to participation was necessary in accordance with the French Jardé's law.

## **2.6 Data analysis**

Statistical analysis and graphs were achieved using the R and Excel programs.

Quantitative variables were described as the mean and standard deviation (SD) or (for skewed distributions) as the median [interquartile range (IQR)]. Qualitative variables were described

as the number (percentage). Finally, we performed a bivariate analysis of independent categorical variables using the  $\chi^2$  test and student test pour for the age variable.

### **3. Results**

#### **3.1 Sample characteristics**

We identified 121 men with a diagnosis of osteoporosis and a BMD T-score < -2.5 who benefited from a geriatric consultation during the study period.

The demographic and medical characteristics of the patients are presented in Table I.

The average age of this population was 85 years old (Standard Deviation: 7).

Of particular notice, the two most common fracture sites in our patient population were vertebral fractures in 66% of cases, and femoral neck fractures in 23% of cases; a majority of our patient population suffered from common geriatric syndromes, in particular 83% of the included patients had a history of falling and 56% of patients were diagnosed with dementia.

#### **3.2 Findings**

##### **3.2.1 Different variables are associated with the completion of an etiological investigation:**

The results of the bivariate analysis are presented in Table II.

Patients with a history of falling ( $p = 0.050$ ), a follow-up in rheumatology or in endocrinology ( $p < 0.0001$ ) or a treatment for osteoporosis ( $p < 0.0001$ ) were more likely to have had an etiological assessment. Conversely, the analysis showed that fracture history ( $p = 1$ ), or the history of dementia ( $p = 0.06$ ), and age ( $p = 0.06$ ) were factors that were not associated the realization of an etiological assessment. There was however, a trend for less investigations in demented patients.

### **3.2.2 For more than half of the patients having benefited an etiological exploration, an etiology for osteoporosis or a bone fragility condition (other than osteoporosis) was identified:**

Of the patients included in the study, 51 (42%) had benefited from first line etiologic investigations. The etiologies for bone fragility found in patients who had investigations are presented in Table III. Of the 51 patients with etiologic investigations, 30 (58,8%) had one or more identified secondary etiologies of osteoporosis or other cause of bone fragility.

Regarding the etiologies identified, the 3 most frequent etiologies were: a history of long-term corticosteroid treatment (17,6% of patients), iatrogenic hypogonadism (13,7% of patients), and late-onset hypogonadism (LOH) (11,8% of patients). Other conditions inducing bone fragility and identified in our study were: primary hyperparathyroidism (7,8% of patients), hyperthyroidism (3,9% of patients) and malignant hemopathies (including myeloma) (3,9% of patients). The iatrogenic causes of osteoporosis found in our study were corticosteroid therapy and hypogonadal hormonal therapy (GnRH analogues) prescribed in prostate cancer.

## **4. Discussion**

Our data reveal that in our geriatric department, etiological assessment for bone fragility and osteoporosis in older men remains insufficient. A little less than half (42%) of the patients in our study population were screened in accord with the recommendations. Evidence from the literature verified that etiological assessments for osteoporosis in men was not only cost-effective, but also improved management outcome of osteoporosis [12]. Nonetheless, still too few men benefited this assessment in our study population. An earlier study conducted by Ryan et al. on a retrospective American cohort of men above the age of 45, revealed that 45% of men had an undiagnosed secondary cause to osteoporosis. And in men with known

secondary osteoporosis at the time of referral, further testing discovered additional causes of osteoporosis in 51% of cases [18].

Our study differs from previous studies in that it assessed whether etiological explorations were done in patients with a diagnosis of osteoporosis in patients seen at 'non dedicated' consultation. Most other studies we encountered in our literature search included patients seen in an osteoporosis specialized clinic or assessed whether osteoporosis was looked for in patients with a disease at risk of causing bone fragility.

The patients were included from all consultations of the geriatric hospital 'Les Bateliers'. Yet, depending on the focus (memory, standardized geriatric evaluation, falls assessment) of each consultation, there was more or less emphasis put on osteoporosis compared with other elements of evaluation which may explain the low rate of etiological explorations in general in our study. We did not specify in our data collection the consultation focus to which the patients came to. Indeed, in "memory" consultations for example, during which the doctor concentrated mainly on the cognitive disorders, its diagnosis, evolution and support needed for the patient, his caregiver(s), it was not always possible to review and reassess the complete patient's medical history.

This could also explain the strong tendency showed in our study to not perform etiological examinations in patients with dementia as these were most certainly patients seen at the memory consult.

The bivariate analysis also revealed a significant difference in the presence or absence of an etiological assessment depending on whether or not the patient had a history of falling. This could be explained by the fact that in our study, fallers were probably mostly seen in specialized falling assessment consultation during which the history of osteoporosis was more systematically sought. This is in line with the previous argument.

Our study revealed that a greater proportion of patients received a treatment for their osteoporosis than those completing etiological explorations of osteoporosis. This suggests that some patients were treated empirically, without etiological assessment of the bone disease. This certainly participated in the under-diagnosis of secondary osteoporosis and pathologies underlying bone fragility. As mentioned earlier, this could explain in part the lesser efficiency of osteoporotic treatment.

The bivariate analysis suggested that patients receiving treatment for osteoporosis more often had etiological investigations, which again demonstrates that etiological assessment and treatment tend to go hand in hand.

Patients managed in endocrinology or rheumatology had significantly more etiological investigations. This was consistent with the fact that patients were referred to these specialties for consultation, for osteoporotic diagnosis and its specific care.

Even if patients were not referred to geriatrics for the exploration of osteoporosis, the fact that it could cause geriatric syndromes (chronic pain, gait disorders ...) and initiate dependency must encourage practitioners, and geriatricians to actively take charge of it.

#### **4.1 Strengths and Limits**

Among our strong points, the size of the sample allowed this retrospective study to be representative of the geriatric population with a diagnosis of osteoporosis. Our geriatric patient population with a mean age of 85 is also a strength of our study as there is a lack of data on the bone health of the oldest old, increasingly suggested to be an approximation for global health.

The proportion of patients with a secondary etiology of osteoporosis and their distribution was consistent with data found in the literature [9]. A study in 220 men with symptomatic

vertebral fractures found a secondary cause in 52% of cases [17]. Another study in 154 men identified 47% patients with secondary osteoporosis [18].

Our study had limits as it was a retrospective and observational survey of a cohort. The collection of data depended on the information present in the hospital medical records. If the etiological assessment had not been conducted at the University Hospital of Lille and/or if the results were not entered in the patient electronic health records, we could not acknowledge them and a patient might have been wrongly classified as not having an etiological assessment of osteoporosis. In regards to the selection criteria, given the absence of ICD-10 coding at the consultation, patients with osteoporosis who had never been hospitalized at the University Hospital of Lille could not be included in the study. This can induce a selection bias.

In addition, our 2-step inclusion method (ICD-10 coding AND presence of a BMD measurement in the records) meant to avoid inclusion of patients labeled as osteoporotic only for billing purposes, exposed us to the risk of excluding patients with osteoporosis and T-scores  $>-2.5$ . This could have induced a bias of selection and misclassification.

In our results we describe that 21 out of 51 patients with an etiological assessment for bone fragility have no etiology identified. Because of the nature of the study, some of the patients may have been wrongly classified as having a primary osteoporosis (no etiology identified). In most cases, there was little information on second line assessment (to eliminate hemochromatosis, mastocytosis, hypercorticism, osteomalacia for example) in the reviewed electronic health records. Such assessments may have identified conditions leading to bone fragility other than osteoporosis in these 21 patients.

We also must point out that our statistically significant results often had a  $p$  value approaching 0.005. Our results will need to be confirmed in a study with a greater patient population to increase statistical power.

With respect to the type of population recruited: a significant part of the recruitment of the consultation patients was done through orthopedic hospitalization services and rheumatology following fracture (among which, the femoral neck fracture was the most common) and requiring surgical management. This could have induced a recruitment bias and explained that the prevalence of femoral neck fracture in our population was greater than that reported in the literature.

## **5. Conclusion and perspective**

Endocrinologists, Rhumatologists and Geriatricians are at the forefront of the management of bone fragility and more specifically, osteoporosis. Etiological explorations of male osteoporosis can improve management of osteoporosis in men. Specific treatments for osteoporosis depending on the etiology exist. Targeted treatment adapted to the etiology of osteoporosis provides better results and better bone remineralization [15]. We must therefore aim to explore more widely the secondary etiologies of osteoporosis in men, work closely with and encourage Geriatric colleagues to do the same in order to better adapt treatment and management. For example, Fracture Liaison Services, such as the one implemented at Lille University hospital since 2016, which is a cooperation between Geriatrics and Rhumatology departments has improved secondary prevention of osteoporotic fractures and long-term persistence for osteoporosis treatments [19, 20]. Possibly, a better knowledge and information of the recommended, standardized etiological assessment for osteoporosis and generalization of a dedicated consultation within the geriatric sector could improve osteoporosis management.

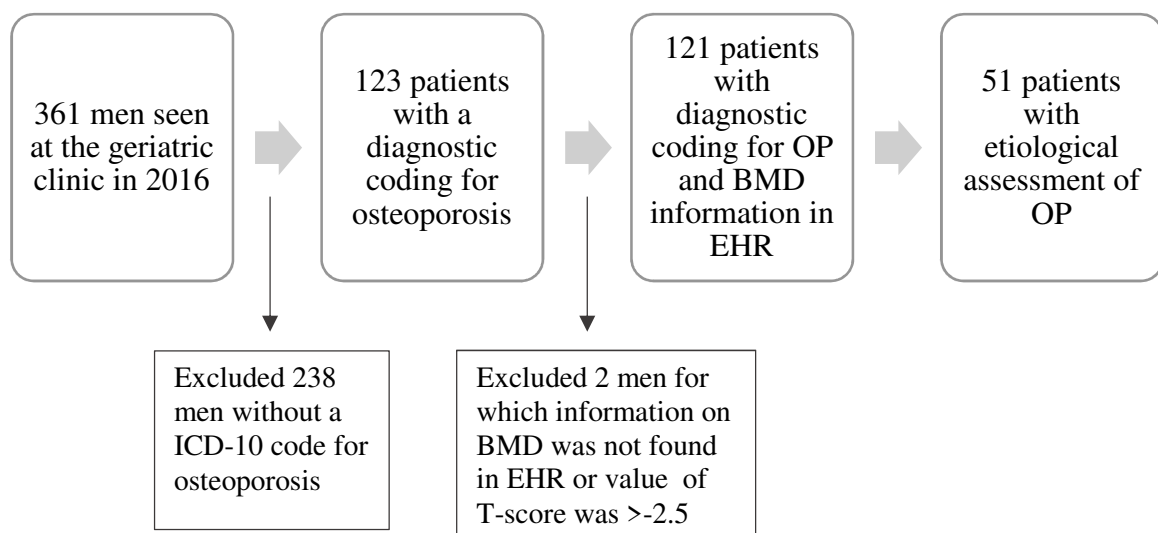
The authors declare no conflict of interest.

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Flow Chart describing patient inclusion in the retrospective observational study. EHR : Electronic Health Records ; OP : osteoporosis

Baseline characteristics of the study population	Patients	
	<i>N</i> = 121	%
Age in years (mean and standard deviation)	85 (7)	

Etiological assessment completed	51	42
Osteoporosis Treatment	64	53
Specialized follow-up (rheumatology, endocrinology)	53	44
History of fracture	107	88
-vertebral fracture	80	66
-femoral neck fracture	28	23
-pelvic fractures	3	2
History of falling	101	83
History of dementia	68	56

Table I : Baseline characteristics of the patient population

Population characteristics	Etiological assessment				Missing Data <i>N</i>	p***
	Yes		No			
	<i>N</i>	%	<i>N</i>	%		
Age						0,0618 (t test)
Specialized follow-up (rheumatology, endocrinology)	41	77	12	22	1	2,32x10 <sup>-11</sup>
History of fracture	47	44	60	56	6	1
History of dementia	23	34	45	66	0	0,055
History of falling	39	39	62	61	2	0,050

Table II : Variables associated with the completion of an etiological investigation, results of the bivariate analysis

Etiology	Patients	
	<i>N</i> =51	%

<b>Iatrogenic origin</b>		
Long-term steroid therapy	9	17,6
LHRH analogues	7	13,7
<b>Pathologies</b>		
Late Onset Hypogonadism	6	11,8
Primary hyperparathyroidism	4	7,8
Hyperthyroidism	2	3,9
Malignant hemopathies (incl. myeloma)	2	3,9
Bone metastasis	2	3,9
<b>No etiology</b>	21	41,2
<b>Total: With identified etiology</b>	30	58,8

Table III : Identification of the aetiologies for bone fragility in our patient population who underwent successful first-line etiological assessment  
 To note that 2 patients had 2 aetiologies to their bone fragility