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Acromegaly is associated with vertebral deformations but not vertebral fractures: results of a cross-sectional monocentric study

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Abstract

Objectives Patients with acromegaly appear to be at increased risk of vertebral fractures despite normal bone mineral density. We investigated the prevalence of vertebral fractures in a cohort of acromegalic patients under 80 years of age.

Methods: Monocentric cross-sectional study performed at Nantes University Hospital from 1998 to 2008. Fifty patients (18 females, 32 males) with a median age of 52.3 years (range: 27-78) were included. Radiological vertebral fractures were evaluated on conventional lumbar and thoracic spine radiographs using Genant's semiquantitative fracture assessment. We studied qualitative abnormalities of the spine using three criteria: osteophytes, disc-space narrowing and wedge-shaped vertebrae. We analysed bone mineral density and endocrine status.

Results: Three patients (6%) had a vertebral fracture: one grade 1 and two grade 2 according to Genant's assessment, with two osteoporotic and one osteopenic patients. They had no unsubstituted pituitary deficiency. Considering the frank deformations (osteophyte or disc narrowing ≥ grade 2 or wedge-shaped), the thoracic spine was deformed in 22 patients (44%) and the lumbar spine in 21 patients (42%).

Conclusion: Acromegalic patients had a low prevalence of vertebral fractures but had a significant amount of vertebral deformations. We speculate that this high prevalence of frank deformations could explain the previously reported high prevalence of vertebral fractures.

Keywords: Acromegaly; Bone; Spine; Spinal fractures; Growth Hormone; Bone density.

1. Introduction

Acromegaly is a rare disease with an estimated prevalence of 2.9 to 13.7 cases per 100,000 persons [1]. It is caused by pituitary adenoma secreting growth hormone (GH) and results in hypersecretion of GH and IGF-1. The average age on diagnosis is 50 years, with an estimated average time to diagnosis of four and a half to five years. Clinical signs are often insidious with a delayed diagnosis in most of the cases. The diagnosis is biologically confirmed by increased plasma IGF-1 levels for age and sex and an absence of GH suppression after an oral glucose tolerance test. Complications of acromegaly are numerous: endocrinological, pneumological, cardiological, gastroenterological and rheumatologic. The latter affects the patient's quality of life.

GH and IGF-1 are closely related to bone metabolism [2]. GH and IGF-1 enable long bone growth, bone maturation and bone mass acquisition in the prepubertal period. In adulthood, they are important regulators of bone homeostasis stimulating osteoformation and mineralization [3,4]. Transgenic murine models with excess GH have shown increased length and diameter of bone and increased bone mineral density (BMD). The thickness of the cortical bone is decreased and the trabecular volume is increased [5] leading to decreased mechanical properties [6] with a decrease in the maximum load supported and a decrease in the tensile strength of the femurs of these mice. Fracture risk in acromegalic patients remains a controversial issue. Some authors have found reduced vertebral and non-vertebral fractures in acromegalic patients with a ratio of 0.41 compared with control subjects [7], while others have found a high rate of vertebral fractures (VF) [8],[9]. A 2015 meta-analysis reported a VF frequency of 38% in acromegalic patients with an odds ratio of 8.26 compared with sex and age-matched controls [10]. Interestingly, there are spinal deformations that are typical of

acromegaly, classically known as Erdheim spondylosis, including anterior and lateral osteophyte castings resulting in an increase in the anteroposterior diameter of the vertebral bodies, false platyspondyly with a biconcave appearance [11]. These deformations have been poorly described in the literature whereas they are major confounding factors in the diagnosis of VF. In this context, we questioned the prevalence of vertebral fractures in acromegalic patients treated at Nantes University Hospital, with a special focus on qualitative analysis of spinal radiographs including description of spinal deformations other than VF.

2. Methods

2.1. Patients

We consecutively recruited patients with acromegaly treated at Nantes University Hospital between January 1988 and January 2018 in a cross-sectional monocentric study. Patients older than 80 years and/or with pathological fractures (secondary to bone metastasis) were not included in the current analysis. Rheumatologic assessment including spine X-rays and bone densitometry had to be within three years of inclusion. The study was approved by GNEDS (Groupe Nantais d'Ethique dans le Domaine de la Santé). Consent has been obtained from each patient or subject after full explanation of the purpose and nature of all procedures used.

2.2. Assessment of vertebral fractures using Genant's semiquantitative method

Our primary endpoint was the radiological prevalence of vertebral fractures. Antero-posterior and lateral x-ray examinations of the thoracic and lumbar spine with Genant's semiquantitative method [12] were performed by two experienced blinded rheumatologists (PG and CP) [Appendix A, Fig. S1; See the supplementary material associated with this article

online]. In case of discrepancy, a third reading was performed by another rheumatologist to reach a consensus among the 3 readers. Fractures were graded as grade 1, 2 or 3 based on anterior, middle or posterior vertebral height ratio decreases of 20-25%, 25-40% and > 40% respectively.

2.3. Non-vertebral fractures

We collected patient histories of non-vertebral fractures including their locations and kinetics via a structured questionnaire.

2.4. Vertebral deformations other than vertebral fractures

As a secondary endpoint, we analysed vertebral deformations with 3 criteria: osteophytes, disc-space narrowing and wedge-shaped vertebrae (Fig. 1). Osteophytes were classified as follows: grade 0: absence of osteophyte, grade 1: intermediate, grade 2: presence without bone bridge and grade 3: presence of bone bridge. Disc-space narrowing was classified as grade 1, 2 or 3 based on the decrease in intervertebral space <50%, 50%-80% and >80% respectively. Wedge vertebrae were defined by a decrease in anterior vertebral height of less than 20%. These three criteria were analysed in the lumbar and thoracic spine except for disc-space narrowing which was not analysed on the thoracic spine owing to the difficulty of interpretation at this level. Deformations were considered as diffuse if they were present on at least three vertebral levels. Radiographs were interpreted by two experienced blinded rheumatologists with the help of an atlas [13]. Interobserver agreement was calculated. The lowest result of the two readings was retained for the analysis to avoid overestimation of these deformations.

2.5. Bone mineral density (BMD)

BMD was measured at the lumbar spine (L1-L4), total hip and femoral neck using dual-energy x-ray absorptiometry (Lunar Prodigy Advance, PA 41532, GE Healthcare Lunar). We used Z-score to compare patients. T-score was used for individual analyses in postmenopausal women and men over 50. BMD was considered low if Z-score $\leq$ -2 SD. WHO criteria for the diagnosis of osteoporosis were used (osteopenia: T-score between -1 and -2.5 SD; osteoporosis: T-score lower than -2.5 SD). Lower hip value was considered when bilateral measurement was available.

2.6. Endocrinological status

Acromegaly was defined as controlled if plasma IGF-1 level was in the reference ranges for age and sex. ACTH deficiency was defined as cortisol <50µg/L with normal or low ACTH at 8 am. In case of intermediate cortisol values between 50 and 180µg/L, an insulin tolerance test was proposed and the result was considered normal if cortisol peak was greater than 180µg/L. TSH deficiency was defined as a free T4 level below the normal laboratory reference ranges with a normal or low TSH level. Men with compatible symptoms (decreased libido, erectile dysfunction) and testosterone concentration below the normal laboratory reference ranges were considered as hypogonadal. Women with amenorrhoea or oligomenorrhea and low FSH and LH levels were considered as hypogonadal. Women with secondary amenorrhea with FSH > 20mUI/mL were considered as menopausal. Hyperprolactinaemia was defined as prolactin levels > 20ng/mL.

2.7. Statistical analysis

All data are expressed as numbers (%) and mean ± SD unless otherwise stated. Univariate comparisons of continuous variables were examined using unpaired *t*-tests or Mann Whitney test when considering low numbers of observations. Categorical variables were compared using Chi2 or Fisher exact tests, when considering low numbers of observations. Statistical significance was assumed when $P \leq 0.05$. Statistical analyses were performed with R software (v.3.5.2) and JMP 14.1.0.

3. Results

3.1. Patient characteristics

Fifty-five patients met the inclusion criteria and were included in the study. Five patients were excluded: three refused to participate, one had bone metastases, one had secreting metastatic adrenocortical carcinoma (Fig. 2). We therefore included 50 patients, 18 women (36%) and 32 men (64%). The average BMI on diagnosis was 26.9 ± 7.1 kg/m². The mean estimated time to diagnosis of acromegaly was 6.9 ± 4.5 years and the mean age on diagnosis was 41 ± 14 years (Table 1).

3.2. Endocrine results

At the time of diagnosis

Patients presented somatotroph macroadenoma (>10 mm) in 80% of the cases (40/50). There were 19 out of 44 patients who presented cavernous sinus invasion (43.2%, six missing data). One patient had MEN1 mutation, none had AIP mutation (tested in 16 and 23 patients respectively). The average IGF-1 concentration on diagnosis was 2.7 ±1.1 times the upper

limit for age and the median (Interquartile range) GH concentration on diagnosis was 19.1 µg/L (35.3). Medical treatment before surgery was used in 24 patients (48%), with somatostatin analogs in 22. 41 patients had surgery (82%). Of these, 30 patients (73.2%) required postoperative drug therapy and 11 (22%) radiotherapy (Table 1).

Status at rheumatological evaluation

There were 28 patients (56%) who had controlled acromegaly at rheumatological evaluation. Thirteen patients (26%) had central hypogonadism – all were supplemented (12 men between 29 and 60 years of age and one 45-year-old woman). Among the women, 14 out of 18 (77.8%) were menopausal. Fourteen patients (28%) had central hypothyroidism, 13 of whom were supplemented with an average dose of levothyroxine of 127 µg/day (50 to 250 µg/day). Eight patients (16%) had ACTH deficiency, all supplemented, with an average dose of hydrocortisone of 17 mg/d (10-30 mg/d). Five patients (10.4%) had transient postoperative diabetes insipidus (Appendix A, Table S1).

Study participants had classically described acromegaly-related complications: diabetes (11 patients), left ventricular hypertrophy (10 patients), sleep apnoea-hypopnoea syndrome (16 patients including 11 treated patients), benign colon polyps (22 patients), carpal tunnel syndrome (15 patients), nodular goitre (23 patients). Only one case of thyroid cancer (pT2N0M0R0) was reported. No patient had colon cancer (Appendix A, Table S1).

3.3. Rheumatological results

Prevalence of vertebral fractures

A VF was found in three patients, two women and one man (Fig. 3), involving L2 in two cases and T12 in one. The prevalence of radiographic VF in our population was 6% (3/50). -Vertebral fractures (VF) involved the anterior segment of the vertebral body. One fracture was grade 1 according to Genant's classification and two were grade 2. Interobserver agreement was good with a kappa coefficient equal to 0.638. A third reading of the x-rays was performed for three patients owing to doubts about thoracic grade 1 vertebral fractures, refuted on the third reading after consensus of the three readers. Of the three patients with vertebral fractures, none had diabetes, two were postmenopausal women with no other risk factors for osteoporosis, without pituitary insufficiency or hyperprolactinemia. For one of them aged 36, it was a post-traumatic fracture. Only one patient, aged 55, did not have a controlled acromegaly owing to initial refusal of treatment. The third patient, aged 59, was a man with several risk factors for osteoporosis: substituted hypogonadism, hyperprolactinemia, tobacco and alcohol consumption. Their common point was the low bone mineral density. Of note, the lumbar T-score was lower in those with VF compared with those without: -2.1 SDS (-3.2 to -2.0) and 0.7 SDS (-1.35 to 1.2), respectively; $P = 0.0191$. In addition, patients with VF were younger than those without: 55 years (36 to 59) and 65 years (55 to 77), respectively; $P = 0.0697$.

Vertebral deformations

At the thoracic and lumbar level, 92% of the patients had at least one criterion for vertebral deformation (osteophytosis, narrowing or wedge-shaped disc). These deformations were

diffuse (present on at least three vertebral levels) in 31/50 (62%) on the thoracic level and in 20/50 (40%) on the lumbar level (Table 2). The frank deformations were significantly associated with younger age. Endocrine factors and BMD were not significantly associated with frank deformations (Table 3). The Kappa coefficient was calculated to analyse interobserver agreement. Interobserver agreement was very good. At the thoracic stage, the overall kappa coefficient including chest deformation on at least three levels, osteophytes and wedge-shaped vertebrae was 0.968. At the lumbar level, the overall kappa coefficient including lumbar deformation on at least three levels, osteophytes, disc space narrowing and wedge-shaped vertebrae was 0.878.

Bone mineral density (BMD)

Most patients had normal BMD. The median (IQR) Z-score at the femoral necks was 0.1 (2.6) and 0.5 (1.6) at the L1-L4 spine. There were 22% of the patients who presented low BMD with a Z-score lower than or equal to -2 SDS.

Non-vertebral fractures

A history of non-vertebral peripheral fractures was reported in 14/43 patients (32.6%). None of these fractures was osteoporotic because all were traumatic peripheral fractures including four ankles and four wrists.

4. Discussion

In a cross-sectional approach of consecutively recruited patients with acromegaly, we found a low prevalence of 6% of radiographic vertebral fractures but a high prevalence of vertebral deformations other than vertebral fractures. This point had not been adequately-studied up

to this point and could well represent a confounding factor in the relationship between VF and acromegaly. The prevalence of 6% in our study population is rather low compared with previous reports. When performing a systematic review of this question, we found that 14 studies have focused on VF in acromegaly [9,10,14–25]. These are summarized in Appendix A Table S2, with VF prevalence ranging from 11% to 64%. VF are described as more common in men at the thoracic level and are correlated with disease activity and hypogonadism. Few studies have investigated the prevalence of VF in the general population. Most are studies on postmenopausal osteoporotic women. In an epidemiological study, Melton et al. determined the prevalence of radiological vertebral fractures in women over 50 years of age: it increases with age, with 3.8% for women aged 50 to 54, 6% for ages 55 to 59 and 41% for 80 to 84 years [26]. Our own results are very consistent with this report.

Some explanations for the low prevalence of VF in our study population can be proposed. Endocrine status such as hypogonadism, inadequately supplemented ACTH deficiency or hypothyroidism are proven risk factors for VF. Of note, hormone substitution was considered as optimal according to current standards of care. For example, all hypogonadal men and premenopausal women were substituted. In most of the previous studies, hypogonadal patients were frequently unsubstituted (2% to 67%). This could explain the lower prevalence of VF in our patients. The presence of ACTH and TSH deficiency could also have an impact on bone fragility in case of inappropriate substitution. In the present study, 28% of our patients had central hypothyroidism compared with 14% to 53% in other studies. Of our patients, 16% had ACTH deficiency compared with 10% to 57.5% in other studies. Of our patients who were operated, 32.5% had controlled acromegaly three to six months after surgery (versus 53% in the Carbonare study [21], 23.4% in the Mormando study

[17], 12.2% in the Mazziotti study [8] and 50% in the Brzana study [16]). In our cohort, 56% of the acromegaly patients were controlled at the time of rheumatologic evaluation. The three vertebral fractured patients in our cohort had controlled acromegaly for two patients, uncontrolled for one patient. In the literature, BMD is often discordant with fracture risk. It is diminished in cases of associated hypogonadism [9]. Low BMD at the hip would be predictive of VF [27]. In our study, BMD was normal in most of the cases. A significant association between the presence of vertebral fracture and osteoporosis considering the T-score was observed in our study. Of the three fractured patients, two were osteoporotic and one was osteopenic. This emphasizes the importance of rheumatologic evaluation with measurement of bone densitometry during the follow-up of these patients.

In addition to patient characteristics, methodological issues must also be examined. We strongly believe that the method used to diagnose VF is critical. A semi-automatic morphometric analysis was used in the majority of reported studies (8/14 studies). This method consists in numerically placing six points on the vertebral body to measure anterior, mean and posterior height. A VF is defined by a decrease in the ratio of these heights by more than 20%. The placement of the points is partly subjective. Interobserver variation coefficients are acceptable for anterior and posterior heights, but this coefficient of variation is not as good for average height [28]. This method does not differentiate between VF and deformations of another origin and must be coupled with a visual analysis. Grados et al. published a review of the literature analysing the different methods to diagnose radiological VF. They reviewed 149 articles and concluded that Genant's semi-quantitative method was to be considered as the Gold Standard. They advised using the morphometric method only with visual evaluation in order to avoid overestimating vertebral fractures owing to other vertebral

deformations [28], still confirmed in more recent studies[29]. We can therefore speculate that the low prevalence in our study was due to different imaging assessment tools for VF. The grade of VF must also be considered. In the 14 studies on VF prevalence in acromegaly patients, most fractures were grade 1. It has been reported that a slight decrease in vertebral height is not always synonymous with vertebral fracture and does not necessarily have a clinical impact [30]. It is grade 1 fractures that pose diagnostic problems and require a differential diagnosis. When we excluded grade 1 vertebral fractures in the studies in which the grade was mentioned, the prevalence of vertebral fractures was reduced by half (16%). Our VF prevalence of 6% therefore seems to be closer to the reality.

A very important finding in our present work is the presence of deformations in a significant number of patients with acromegaly. Vertebral deformations other than vertebral fractures are poorly described in the literature. Only one study of the 14 described them and reported 81% of degenerative disc disease without specifying the evaluation criteria [16]. The prevalence of so-called frank deformations in our cohort which could have led to the diagnosis of vertebral fracture by semi-automatic reading was 44% in the thoracic spine and 42% in the lumbar spine. These deformations were mainly found at the thoracic level and in men. We propose the hypothesis that these spinal deformations are differential diagnoses of VF. This hypothesis strengthens the fact that any semi-automatic morphometric analysis must be coupled with a visual analysis, especially in populations that are prone to vertebral deformations of other types. It is important to differentiate VF and vertebral deformations to avoid inappropriate treatments. A parallel may be proposed with patients with ankylosing spondylitis. These patients are often young men, frequently have vertebral deformations, especially at the thoracic level, and are at risk for secondary osteoporosis possibly leading to

VF. Many studies have investigated fracture risk in these patients – again finding very variable prevalence of VF. The highest prevalence of VF has been reported in studies using semi-automatic morphometric analysis. This method therefore overestimates the risk of vertebral fractures and does not distinguish vertebral fractures from spinal deformations related to the disease itself [31–33].

Our study has some strengths including the adequate hormonal status. Our study is one of the first to look at vertebral deformations other than vertebral fractures and to quantify them. It sheds light on the methodological issues regarding the diagnosis of VF in patients with acromegaly and suggests that Genant's semiquantitative method should be used when considering VF in such a context instead of the semi-automatic morphometric analysis which probably overestimates them. Some limitations must also be acknowledged. Obviously, our study considered a small number of patients although it is of similar size to most studies on the topic since acromegaly is a rare disease. Larger recruitment could have provided lower confidence intervals for VF prevalence. In addition, our cross-sectional design did not make it possible to study the incidence but only the prevalence of VF.

Appendix A. Supplementary data

Supplementary data (Fig. S1, Table S1-S2) associated with this article can be found in the online version at …

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Declaration of interest

none

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Table I: Endocrinological data and acromegaly management of study participants.

Men	32/50 (64%)
Women	18/50 (36%)
Age (years)	52.7 (± 12.9)
BMI (kg/m²)	28.6 (± 4.3)
Smoking history	19 (41.3%)
Consumption of alcohol	5 (11.6%)
Age on diagnosis (years)	41 (± 14)
Year of diagnosis	
[1988-1998]	10 (20%)
[1999-2009]	10 (20%)
[2010-2018]	30 (60%)
Adenoma characteristics	
Microadenoma	10/50 (20%)
Macroadenoma	40/50 (80%)
Cavernous sinus invasion	19/44 (43.2%)[a]
Hormonal status on diagnosis	
Hyperprolactinaemia	16/42 (38.1%)
Central hypothyroidism	3/49 (6.1%)
Central hypogonadism	7/48 (14.6%)
ACTH deficiency	2/49 (4.1%)
Menopausal women	14/18 (73.8%)
Preoperative medical treatments	24/50 (48%)
Dopaminergic agonists	5 (20.8%)
GH antagonists	2 (8.3%)
Somatostatin analogs	22 (91.7%)
Surgery	41/50 (82%)
Postoperative control at 3-6 months	13/40 (32.5%)
Postoperative treatment	30/41 (73.2%)

Dopaminergic agonists	13 (31.7%)
GH antagonists	2 (4.9%)
Somatostatin analogs	29 (70.7%)
Novel somatostatin analogs	4 (9.8%)
Radiotherapy	11/50 (22%)

Data are mean +/-SD, or numbers (%)

[a] Cavernous sinus invasion could not be ascertained in 6 patients.

Table II: Description of vertebral deformations.

Thoracic deformation	46 (92.0%)
Frank thoracic deformation	**22 (44%)**
Thoracic osteophytes	
grade 0	5 (10.0%)
grade 1	24 (48.0%)
grade 2	15 (30.0%)
grade 3	6 (12.0%)
Thoracic wedge-shaped	14 (28.0%)
Diffuse deformation	31 (67.3%)
Lumbar deformation	**46 (92%)**
Frank lumbar deformation	**21 (42%)**
Lumbar osteophytes	
grade 0	9 (18.0%)
grade 1	31 (62.0%)
grade 2	8 (16.0%)
grade 3	2 (4.0%)
Lumbar wedge-shaped	5 (10.0%)
Lumbar disc nip	
grade 0	8 (16.0%)
grade 1	24 (48.0%)
grade 2	17 (34.0%)
grade 3	1 (2.0%)
Diffuse deformation	20 (40.0%)

Data are numbers (%)

Patients were considered deformed if they had at least one of the deformation criteria (for the thoracic stage: osteophytes, wedge-shaped, for the lumbar stage: osteophytes, wedge-shaped, disc nip). Deformation was defined as frank if at least 1 of the deformation criteria (osteophytes or disc nip) was greater than or equal to grade 2 or wedge-shaped. For each criterion, the less severe result of the 2 observers was considered.

Table III: Comparison of patients with or without vertebral deformations.

Variables	Patients with frank-deformation (n=31)	Patients without frank-deformation (N=19)	*P*-value
Age (Yrs)	60 ± 13	71 ± 13	0.004
Male sex	18 (58%)	14 (74%)	ns [a]
BMI (Kg/m^2)	26.8 ± 1.5	27.2 ± 1.1	ns
Endocrinological data			
Central hypogonadism	8 (26%)	5 (26%)	ns [b]
Central hypothyroidism	6 (19%)	8 (42%)	ns [b]
ACTH insufficiency	4 (13%)	4 (21%)	ns [b]
Menopause	2 (50%)	11 (79%)	ns [b]
Controlled acromegaly	19 (61%)	11 (65%)	ns [a]
Bone mineral density			
Z-Score (SDS)	-0.5 (-1.9 to 0.3)	-0.5 (-2.2 to 0.1)	ns
Z-score $\leq$ -2,0	6 (19%)	5 (26%)	ns [a]

Data are mean SD or numbers (%) or median (25th to 75th percentile) when specified. [a] Chi 2 test and [b] Fisher exact test.

Figure 1: Vertebral deformations - Radiographic examples from study participants

Figure 2: Flow Chart

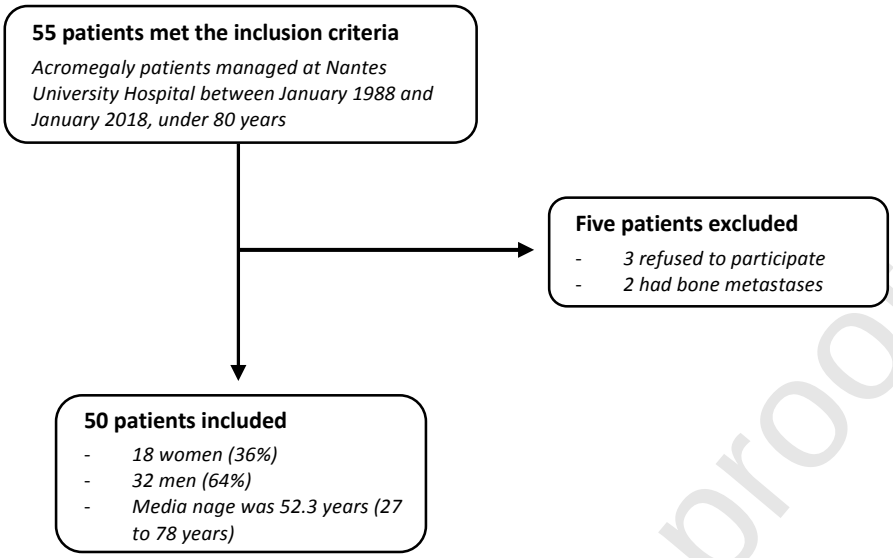


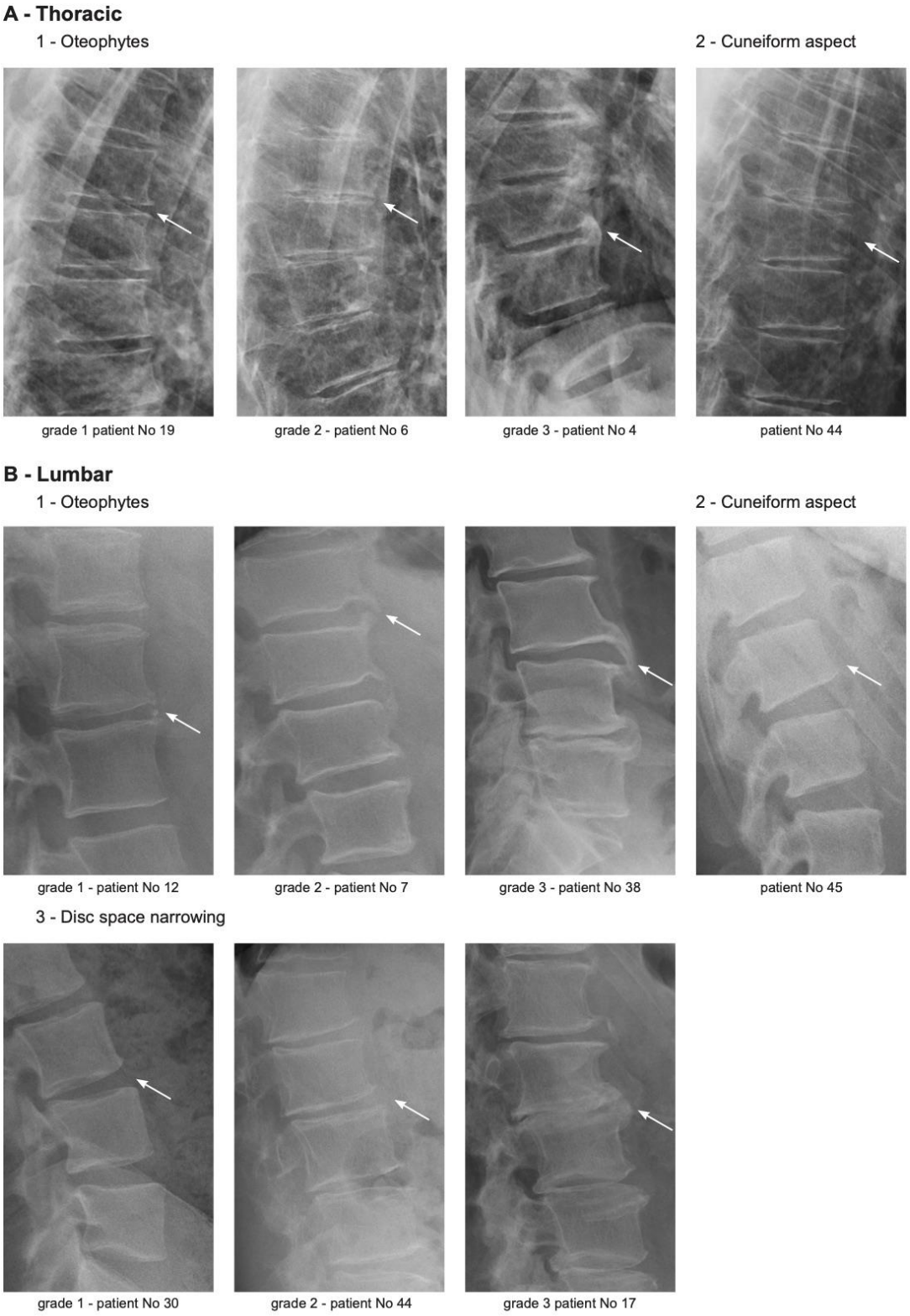
Figure 3: X-rays of fractured patients

1: Vertebral Fracture L2 grade 2

2: Vertebral Fracture L2 grade 1

3: Vertebral Fracture T12 grade 2

Figr-1


A - Thoracic
1 - Oteophytes
2 - Cuneiform aspect
grade 1 patient No 19
grade 2 - patient No 6
grade 3 - patient No 4
patient No 44
B - Lumbar
1 - Oteophytes
2 - Cuneiform aspect
grade 1 - patient No 12
grade 2 - patient No 7
grade 3 - patient No 38
patient No 45
3 - Disc space narrowing
grade 1 - patient No 30
grade 2 - patient No 44
grade 3 patient No 17

Figr-2