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Aurore Nottez[1], Sami Kolta[2], Georges Lion[3], Camille Ternynck[4], Isabelle Legroux-Gérot[5], Marie-Christine Vantyghem[6], Bernard Cortet[5], Julien Paccou[5]

Affiliations:

[1] Univ. Lille, CHU Lille, Department of Rheumatology, 59000 Lille, France

[2] Department of Rheumatology, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France; INSERM UMR-1153, Paris, France

[3] Univ. Lille, CHU Lille, Department of Nuclear Medicine, 59000 Lille, France

[4] Univ. Lille, CHU Lille, ULR 2694 - METRICS : Évaluation des technologies de santé et des pratiques médicales, F-59000 Lille, France

[5] Univ. Lille, CHU Lille, EA 4490, Department of Rheumatology, 59000 Lille, France

[6] Univ. Lille, CHU Lille, Department of Endocrinology, Diabetology, Metabolism, Nutrition, 59000 Lille, France

Corresponding author:

Julien Paccou, MD, PhD

PMOI EA 4490, Department of Rheumatology

CHU Lille, 2, avenue Oscar Lambret - 59037 Lille Cedex, France.

Email: julien.paccou@chru-lille.fr

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ABSTRACT

Introduction

Reports of elevated bone mass (EBM) on routine DXA scanning are not infrequent. However, epidemiological studies of EBM are few in number and definition thresholds variable. The purpose of this study was to assess the prevalence and causes of EBM in the general population referred to a single university hospital – catering for a population of 5.9 million inhabitants – for DXA scanning.

Material and methods

DXA databases were initially searched for individuals with a bone mineral density (BMD) Z-score ≥+4 at any site in the lumbar spine or hip from April 1st, 2008 to April 30st, 2018. Two Hologic scanners were available at the Lille University Hospital (France). Prevalence of EBM was evaluated, as were causes associated with EBM.

Results

At the lumbar spine, 18,229 bone density tests were performed in women and 10,209 in men. At the hip, 17,390 tests were performed in women and 9,857 in men. The total number of patients who had at least one bone density test was 14,745, of which 64.2% were female. Of these 14,745 patients, 211 had a Z-score ≥+4 at any site, i.e. a prevalence of 1.43% [1.25%-1.64%]. The DXA scans and medical records of 92 men and 119 women with elevated BMD were reviewed to assess causes. An artefactual cause was found in 164 patients (75%) with EBM (mostly degenerative disease of the spine), and an acquired cause of focal EBM was found in only 2 patients, both of whom had sclerotic bone metastases from prostate cancer. An acquired cause of generalized EBM was found in 32 patients (15%), the vast majority of whom had renal osteodystrophy (n=11), followed by hematological disorders (n=9; e.g. myeloproliferative syndromes and mastocytosis) and diffuse bone metastases from solid cancer (n=5). Of the remaining causes, rare hereditary diseases (e.g. osteopetrosis...) and unexplained EBM were found in 10 and 6 cases respectively.

Conclusion

The prevalence of EBM (Z-score ≥+4 at any site) was 1.43% [1.25%-1.64%]. In nearly all instances (97.1%) the explanation for EBM could be found in the medical record and through conventional investigations. This study suggests that the main cause of EBM is degenerative

disease of the spine. Further studies are needed to differentiate artefactual EBM from hereditary or acquired EBM, and to investigate unexplained EBM. Genetic testing may prove useful in elucidating rare unknown causes.

INTRODUCTION

Although elevated bone mass (EBM) or dense bone diseases may be suspected when standard radiographs show abnormally dense bone, measuring bone mineral density (BMD, g/cm²) using dual-energy X-ray absorptiometry (DXA) is not only far more accurate, but also quantifies the increase in bone mass **(1)**. Although no consensus exists on the definition of EBM, several BMD Z-/T-score cut-offs values have been suggested. In 2005, Michael Whyte **(1)** proposed that a Z-score > + 2.5 should be used. Before that, varying cut-offs were used in case reports and case series. A T- and/or Z-score cut-off of ≥ + 4 at the lumbar spine or hip was used in a study of 335,115 DXA scans from 15 centres in the UK **(2)**. Using that cut-off, the prevalence of EBM in that study was 5/1000.

Careful review of DXA reports and images often reveals that the increase in BMD can be potentially attributed to artefactual causes, such as degenerative disease of the spine (with or without scoliosis), vascular calcifications (most notably of the abdominal aorta), syndesmophytes, diffuse idiopathic skeletal hyperostosis (DISH), and implanted material (e.g., vascular prosthesis or vertebroplasty) **(3,4)**. In the above-mentioned British multi-centre study, about 50% of cases of EBM were due to degenerative disease **(2)**. Lesions responsible for focal EBM should be considered as dictated by the clinical setting. These lesions include sclerotic bone metastases, Paget's disease, and fibrous dysplasia of bone **(5–9)**.

The causes of acquired generalized EBM are both numerous and varied. Nutritional causes include an excessive intake of fluoride **(5)**. A well-established metabolic cause is renal osteodystrophy, in which the bone sclerosis predominantly affects the axial skeleton **(6)**. Endocrine causes include chronic hypoparathyroidism and pseudo-hypoparathyroidism **(7)**. Among hematological disorders, mastocytosis and myeloproliferative syndromes have been reported to cause EBM **(8,9)**. Leukaemia, lymphoma, diffuse bone metastases from solid cancer, and the very rare cases of sclerotic multiple myeloma are the main malignant causes of EBM **(10)**. Hepatitis C can cause diffuse osteosclerosis **(11,12)**. Obesity has been suggested as a possible cause of EBM **(13)**.

Several genetic diseases are associated with a generalized increase in BMD, chief of which are osteopetrosis, mutations in the SOST gene, and mutations in the LRP5 and LRP6 genes. The quantitative and qualitative bone abnormalities seen in these diseases have variable effects on bone strength and fracture risk, even though BMD values are usually extremely high, with Z-scores that can exceed + 6 at the hip and lumbar spine **(14–21)**.

In clinical practice, reports of EBM on routine DXA scanning are not uncommon, and the causes are both numerous and varied. However, most of the published data are from case series and the prevalence of EBM remains largely unknown.

The purpose of this study was to evaluate the prevalence and causes of EBM in adult patients who underwent DXA scanning at Lille University Hospital, Lille, France over a 10-year period.

PATIENTS AND METHODS

Study design

Our study was conducted on a retrospective cohort of subjects included from April 1st, 2008 to April 30th, 2018. All of the patients were adults (age ≥18 years) who had successfully undergone at least one DXA scan to determine BMD. During the study period, two Hologic© scanners were available at Lille University Hospital (HOLOGIC Discovery A S/N 81360 and HOLOGIC Horizon W S/N 300869M). The study protocol was approved by the local Institutional Review Board (n° DEC2018-349), and the study procedures complied with the Helsinki Declaration of 1975, as revised in 2000.

Definition of elevated bone mass

Elevated bone mass was defined as a Z-score ≥+4 at any site in the lumbar spine or hip in order to compare our findings with those reported by Gregson CL *et al.* **(2)**.

Data extraction

An anonymised file with data on all DXA scans was extracted from each Hologic© scanner. Two databases were obtained. Neither of them contained any T or Z-score data. DXA scan results were expressed in g/cm² for all assessed sites (e.g., the value in g/cm² for the 4 lumbar vertebrae was provided).

The data were analysed by age group – 18 to 34.9 years, 35 to 39.9 years, 40 to 44.9 years, 45 to 49.9 years, 50 to 54.9 years, 55 to 59.9 years, 60 to 64.9 years, 65 to 69.9 years, 70 to 74.9 years, 75 to 79.9 years and ≥ 80 years – using EBM-value thresholds for each age group, firstly among men and then among women. The following reference curves were used: for women, the IOG curve for the lumbar spine (established from three French populations, Isos, Ofely and Genset) **(22)** and the NHANES curve for the hip (National Health and Nutrition

Examination Survey) **(23,24)**; for men, the BMDCS curve for the lumbar spine (Bone Mineral Density in Childhood Study) **(25)** and the NHANES curve for the hip **(23,24)** (e.g., a threshold of 1.401 g/cm² equated to a Z-score ≥+4 for a woman between 45-49.9 years old, according to the IOG reference curve).

EBM-positive DXA scan results (i.e., DXA scan results satisfying the definition of EBM) were selected by gender and age group by the principal investigator (JP) using the reference curves mentioned above.

We determined the total number of DXA scans performed over a 10-year period as well as the corresponding number of patients assessed (since several DXA scans could have been performed for any given patient). We also determined the total number of patients with at least one EBM-positive DXA scan result. If a patient had several EBM-positive DXA scan results, the result of the last scan was selected and used for the analysis.

Data analysis

Review of DXA scan reports and images often provided potential explanations for an artefactual cause of EBM at the lumbar spine. However, medical records and other images of the spine and hip were also examined in order to identify other causes.

An Electronic Case Report Form (eCRF) was completed for each patient with EBM. The following data were collected: gender, age, weight, height, body mass index (BMI) and date of scan. For each site of interest (lumbar spine, femoral neck and total hip), the following data were collected: BMD (g/cm²), T-scores, and Z-scores if available on the DXA scan report. All DXA images with a BMD T- or Z-score ≥+4 at any site were visually inspected by 2 clinicians (JP and AN) trained in the interpretation of DXA scans, and identified causes were recorded. A notation was made if a cause was not identified (unknown causes).

Identified causes fell into the following 4 categories, as proposed by Gregson *et al.* **(2)** and Paccou *et al.* **(3)**: **(i)** artefactual causes, comprising degenerative disease of the spine with or without scoliosis, vascular calcifications, syndesmophytes, DISH, and implanted material (e.g., vascular prosthesis or vertebroplasty); **(ii)** acquired causes of focal EBM, comprising sclerotic bone metastases (e.g., from prostate or breast cancer), Paget's disease, and fibrous dysplasia of bone; **(iii)** acquired causes of generalized EBM, comprising excessive intake of fluoride, renal osteodystrophy, endocrine causes (e.g., chronic hypoparathyroidism, pseudo-hypoparathyroidism…), diffuse bone metastases from solid cancer, hematological disorders

(such as mastocytosis, myeloproliferative syndromes, leukaemia, lymphoma, and the very rare cases of sclerotic multiple myeloma), hepatitis C, and obesity (body mass index ≥ 30); **(iv)** genetic causes, comprising osteopetrosis, sclerosteosis, Van Buchem's disease and LRP5/LRP6 mutations.

Statistical analysis

Data were analysed using SAS software (version 9.4; SAS Institute Inc., Cary, NC). Categorical variables were expressed as numbers (percentages). EBM rates in the overall population and in the population stratified by gender and age group (< 40; [40, 60[; [60, 80[and ≥ 80 years) were estimated with 95% confidence intervals (exact Clopper-Pearson method). EBM rates were compared between genders using a Chi-square test, and between age groups using the Cochran-Armitage test. Statistical testing was performed at the 2-tailed α level of 0.05.

RESULTS

Prevalence of elevated bone mass

Over the 10-year study period, 28,438 DXA scans were performed at the lumbar spine and 27,247 at the hip. Of the 28,438 lumbar spine scans, 18,229 were performed on women and 10,209 on men. Of the 27,247 hip scans, 17,390 were performed on women and 9,857 on men.

The total number of patients who had at least one DXA scan was 14,745, of whom 64.2% were women. Of those patients with at least one DXA scan, 211 had a Z-score ≥+4 at any site, i.e. a prevalence of 1.43% [1.25%-1.64%]. Elevated bone mass was more frequently found in men (1.74% [1.41%-2.13%]) than in women (1.26% [1.04%-1.50%]) (p=0.021). Moreover, our findings indicate that prevalence of EBM is associated with age (p<0.0001). Indeed, when we compared prevalence of EBM across age groups, we found the following: 0.55% [0.31%-0.90%] in patients <40, 1.09% [0.08%-1.40%] in patients 40-59.9, 2.01% [1.66%-2.42%] in patients 60-80 and 2.32% [1.54%-3.33%] in patients >80.

Among those 211 patients, EBM at lumbar spine alone was found in 84% of cases (n=177), at both lumbar spine and femoral neck in 2% of cases (n=5) and at lumbar spine and total hip in only 1% of cases (n=2) **(Figure 1)**. Elevated bone mass at the hip (femoral neck and/or total

hip) was found in 8.5% of cases (n=18). "Diffuse" EBM (affecting the 3 sites) was found in 9 patients (4%).

Patient characteristics

Table 1 shows patients' socio-demographic and disease characteristics. The study included a group of 211 patients who were predominantly female (56%) and Caucasian (98%). Age (mean ± SD) was 63.9 ± 15.5 years. Most of the patients were overweight (33%) or obese (BMI ≥ 30kg/m²) (41%). The main reason for performing DXA scans was to screen for and treat postmenopausal, male or glucocorticoid-induced osteoporosis (n=125, 60%). DXA scans was also frequently performed to screen for and treat secondary osteoporosis in patients who had undergone transplantation (mostly kidney and liver) (n=25, 11%). Lastly, the reason for performing bone density tests was unknown in 19 patients (9%), despite a complete review of the medical records.

Causes of elevated bone mass

In a few patients, EBM was attributed to several causes, which explains the difference between the total number of causes (n=215) and the total number of patients (n=211) **(Figure 2)**.

Elevated bone mass was potentially attributed to artefactual causes in 75% of the patients (n=164). The cause was mainly degenerative disease of the spine (n=137, 63%) with or without another artefactual cause (scoliosis, DISH, vertebral fracture...) (Supplementary figure 1). Other artefactual causes were ankylosing spondylitis in 4 patients (Supplementary figure 2) and obesity (without osteoarthritis) in 8 patients (Supplementary figure 3). Moreover, “diffuse" EBM was found in 3 patients (patients with both hip and spine osteoarthritis) and associated with obesity in 2 of them.

An acquired cause of focal EBM was found in only 2 patients, both of whom had sclerotic bone metastases from prostate cancer at the lumbar spine.

An acquired cause of generalized EBM was found in 15% of the patients (n=32) identified as having EBM (n=215). The causes were renal osteodystrophy (n=11) (Supplementary figure 4) and hematological disorders (myeloproliferative syndromes (n=7), mastocytosis (n=1), and sclerotic multiple myeloma (n=1) (Supplementary figures 5 and 6)). Diffuse bone metastases from solid cancer were found in 5 patients (Supplementary figure 7). Other causes were

hypoparathyroidism (n=2) (Supplementary figure 8), acromegaly (n=1), Erdheim-Chester disease (n=1) and Langerhans cell histiocytosis (n=1) (Supplementary figure 9). In 2 patients, after examination of the DXA scan reports and images and medical records, we concluded that hepatic cirrhosis was the cause of generalized EBM. The first patient was a 62 year-old woman (BMI 29 kg/m^2) with hepatocellular carcinoma secondary to alcoholic cirrhosis (Supplementary figure 10). She had already undergone chemoembolization of the liver and was awaiting a liver transplant (Femoral neck T-score= +3.4 and Z-score= +4.8; Total hip T-score= +3.0 and Z-score= +4.0; Lumbar spine T-score= +6.0 and Z-score= +6.2). The second patient was a 51 year-old woman (BMI 29 kg/m^2) with alcoholic cirrhosis, who had already had a liver transplant. Elevated bone mass was found at the lumbar spine both before and after the transplant (Femoral neck T-score= 0.0 and Z score= +0.9; Total hip T-score= 0.0 and Z-score= +0.4; Lumbar spine T-score= +3.6 and Z score= +4.0).
Moreover, “diffuse" EBM was found in 5 patients as described above. In those patients, EBM was associated with mastocytosis (n=1), myelofibrosis (n=3), and hepatocellular carcinoma secondary to alcoholic cirrhosis (n=1).

A genetic cause was found in 9 patients **(Table 2)**. Causes were autosomal recessive osteopetrosis (carbonic anhydrase II deficiency syndrome) with “diffuse” EBM (n=1) (Supplementary figure 11), X-linked hypophosphatemia (n=1), GATA-binding protein 3 mutation associated with hypoparathyroidism (n=1) and type 1A pseudohypoparathyroidism (n=1). Moreover, two patients were identified with lipodystrophic syndrome (no mutation identified) (Supplementary figure 12), and three patients with type 1 myotonic dystrophy (Steinert's disease) with no other identifiable cause of EBM (Supplementary figure 13).

In 8 patients, the cause of EBM was unknown, even after a careful review of their medical records, but 4 of them had hepatic abnormalities (hepatitis-C negative patients) **(Table 3)**.

DISCUSSION

In this retrospective study conducted at a single university hospital catering to a population of 5.9 million inhabitants, the prevalence of EBM, determined using a Z-score threshold of ≥ +4 at any one of the measurement sites, was found to be 1.43% [1.25%-1.64%]. The prevalence of EBM was higher in men and in older age groups. The main causes of EBM were degenerative disease of the spine, followed by generalized acquired causes including renal osteodystrophy, haematological disorders (e.g. myeloproliferative syndromes,

mastocytosis…) and diffuse bone metastases from solid cancer. Other causes were rare hereditary diseases, some of which were expected (e.g., osteopetrosis, X-linked hypophosphatemia, hypoparathyroidism and pseudohypoparathyroidism) while others were not (Steinerts's disease and Lipodystrophic syndrome). In 8 patients (3.8%), the cause of EBM could not be determined (unknown cause), even after a careful review of their medical records.

To the best of our knowledge, there is only one population-based study on the prevalence of EBM. In that ambispective study, conducted in the UK by Gregson C. *et al* **(2)**, the authors retrospectively analysed the BMD data (Hologic® and Lunar®) from 13 sites across the UK, and conducted a prospective analysis of data from 2 other sites. Overall, they examined a total of 335,115 DXA scans. The Z-score threshold of ≥ +4 was initially described by Little *et al.* **(26)** in a study on patients with EBM due to LRP5 mutations. In that study, the authors reported that the hip and lumbar spine Z-scores of patients with LRP5 mutations exceeded +4. Using this value as a threshold for Z- and T-scores in their study, Gregson C. *et al.* found that 0.42% of the T- and/or Z-scores in their Hologic® population were ≥ +4. As such, there is a difference between the prevalence of EBM reported in that study and the prevalence of EBM found at Lille University Hospital (0.42% versus 1.43%). One explanation for this difference may be related to the fact that the prevalence in the UK study was calculated based on the number of BMD scans performed and not on the number of patients. The difference may also reflect a centre effect since Lille University Hospital is a tertiary centre that caters for a population of 5.9 million inhabitants and recruits patients with specific characteristics (liver and kidney transplantation, rare metabolic diseases, etc.). Moreover, we decided to define EBM in terms of Z-score alone to avoid the trap of T-scores. Indeed, information can be divergent when using T- as well as Z-scores, especially in elderly individuals. And T-scores are irrelevant and misleading when assessing EBM, while Z-scores tell us how far away the individual is from the mean in an age and gender matched population.

Furthermore, in our study, we found that about 75% of the causes of EBM were artefactual, compared to 54% in the study conducted by Gregson *et al.*, even though we used the same classification for artefactual etiologies (with degenerative disease of the spine accounting for 63% of the artefactual causes of EBM in our study vs. 49% in the UK study). The higher number of artefactual causes could also explain the higher prevalence of EBM in our study, in which more BMD tests were carried out at osteosynthesis sites (approximately 6% in our study vs. 1.7%). Among the artefactual causes, the most common cause was degenerative

disease of the spine. It is also important to note that there was a high proportion of overweight (33.2%) and obese (41.2%) patients in our population. The mean BMI of patients with EBM in the study conducted by Gregson *et al.* **(2)** was also high (mean BMI: 31.0 kg/m²). The association between high BMI and EBM has been previously reported **(13,27)**. Indeed, the increase in mechanical stresses related to increased weight could lead to an increase in bone formation. Finally, there are limits to the interpretation of BMD in obese patients due to the measurement technique itself. As DXA is based on the differential attenuation of X-rays by the different tissues in the body, it could indicate an artefactual increase in BMD related to the interposition of fat tissue, particularly at the hip.

Generalized acquired causes were the second most frequent cause of EBM (11%). Among these causes, several have already been reported in the literature in case reports and case series (renal osteodystrophy **(6)**, sclerotic multiple myeloma **(10)**, primary and secondary myelofibrosis **(8)**, mastocytosis **(9)**...). More than half of the patients with "diffuse" EBM in our cohort were in this group. In our study, we found 2 cases of patients with hepatic cirrhosis associated with EBM without any other identified cause of EBM. It is generally accepted that hepatic cirrhosis is associated with osteoporosis. However, hepatitis C has been reported to be associated with EBM in several case reports, and while the underlying pathophysiological mechanisms remain largely unknown **(11,12)**, insulin-like growth factor system abnormalities have been reported in hepatitis C-associated osteosclerosis **(12)**. We can speculate that these pathophysiological mechanisms are not specific to hepatitis C and that hepatic cirrhosis could also be rarely associated with EBM due to the same mechanisms. Additionally, among those patients in our study with an unknown cause of EBM, 4 had liver disease, including hepatic cirrhosis. Our results need to be confirmed in another cohort of patients.

In our study, genetic causes of EBM were quite rare. Indeed, we found only one case of osteopetrosis associated with a mutation of the carbonic anhydrase II gene **(28)**. We also found 3 cases of Steinert's disease. To the best of our knowledge, this is the first time that an association has been reported between Steinert's disease and EBM. Steinert's disease, which is also known as type 1 muscular dystrophy, is an autosomal dominant disorder. It is the most common form of muscular dystrophy in adults and is characterized by a variable phenotype and the involvement of several organs (muscle deficit, heart disorders, cataracts, early baldness, endocrine disorders including hypogonadism and glucose tolerance disorders). Bone impairment in this disease has not been extensively studied. In the only study we found in the literature, the authors compared brain CT scans and lumbar-spine and hip BMDs in 16

patients with Steinert's disease versus 20 controls matched for age and sex **(29)**. They reported hyperostosis of the skull and higher lumbar-spine BMD in patients with Steinert's disease compared to controls. Furthermore, a recent study suggests that BMD parameters are different between type 1 and 2 muscular dystrophy (MD). In that study, patients with type 1 MD were found to have higher total body, lumbar-spine, pelvis, arm and leg BMDs than patients with type 2 MD and age-matched healthy controls **(30)**. These findings need to be confirmed in a large cohort of patients with Steinert's disease, in which bone health assessments – including BMD and bone remodelling markers – are systematically performed. In our study we also found 2 cases of EBM associated with lipodystrophic syndrome. This group of diseases is usually associated with a phenotype characterized by an abnormal distribution of body fat and a dysmetabolic profile with insulin resistance. Many mutations associated with these abnormalities have been identified, and some of them have been reported to be associated with bone impairment. Thus, in a study conducted by Lima *et al.* **(31)**, the authors investigated biological and BMD parameters in a cohort of 21 patients with Berardinelli-Seip syndrome. Berardinelli-Seip syndrome, which is also known as congenital generalized lipodystrophy (CGL), is an autosomal recessive disorder which is classified into 4 different subtypes based on specific genetic mutations **(32,33)**. The authors reported that 12 patients – mainly with type 2 CGL, i.e. a mutation in the BSCL2 gene – had a Z-score $\geq +2.5$ at least at one site.

Study strengths and weaknesses

We acknowledge that there are several limitations to this study. Since the study was hospital-based (rather than population-based), our findings cannot be extrapolated to other populations. Moreover, as the data was from a tertiary centre, they may not be representative of the population as a whole. A major limitation of this type of study, which is inherent to the retrospective and observational character of the cohort, is missing data. For some patients, the cause of EBM was classified as unknown simply because no data (e.g. scans, medical records…) were available. However, as all cases of EBM were reviewed by two rheumatologists with experience in the field of bone disease, and particularly EBM, we were able to determine the cause of EBM in practically all of the patients (96.2%). Moreover, scans and biological assessment were available for most of the patients. Finally, bone assessments were based on DXA alone, without data on bone microarchitecture or fractures history. DXA has its limitations in that it measures only areal BMD. Indeed, DXA scanners generate 2D images of complex 3D structures, and report bone density as the quotient of bone mineral

content and bone area. An obvious pitfall of this method is that a larger bone would indicate superior strength, but may in fact have the same bone density as a smaller bone. Other imaging techniques are available such as peripheral quantitative CT (pQCT) or high resolution peripheral quantitative CT (HRpQCT), but are largely research tools. Furthermore, DXA BMD does not differentiate whether the variation in BMD arises from differences in cortical mass, trabecular mass, or external bone size. Finally, DXA is a widely used, useful and robust tool.

CONCLUSION

Elevated bone mass is a relatively common feature and can have a considerable number of causes, which can often be determined after careful review of DXA scan reports and images. In this study, we found that the main cause of EBM was degenerative disease of the spine. However, our findings suggest that generalized acquired and genetic causes are also possible. Further studies are required to corroborate these findings. A multi-centre French study is currently under way and it is hoped that it will confirm or refute those causes found in our study that have hitherto not been described (e.g., liver cirrhosis) or poorly described (e.g., Steinert's disease and lipodystrophies). However, studies on selectively targeted patient populations (e.g., liver transplantation patients, or patients with Steinert's disease or lipodystrophy syndromes) are needed to confirm or refute certain causes found to be associated with EBM in our study. Ultimately, high bone mass genetic panels could be undertaken after exclusion of well-known causes by chart and radiographic review, in the few remaining patients.

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Figure 1: Number of patients with a T- and/or Z-score ≥ +4 according to studied site

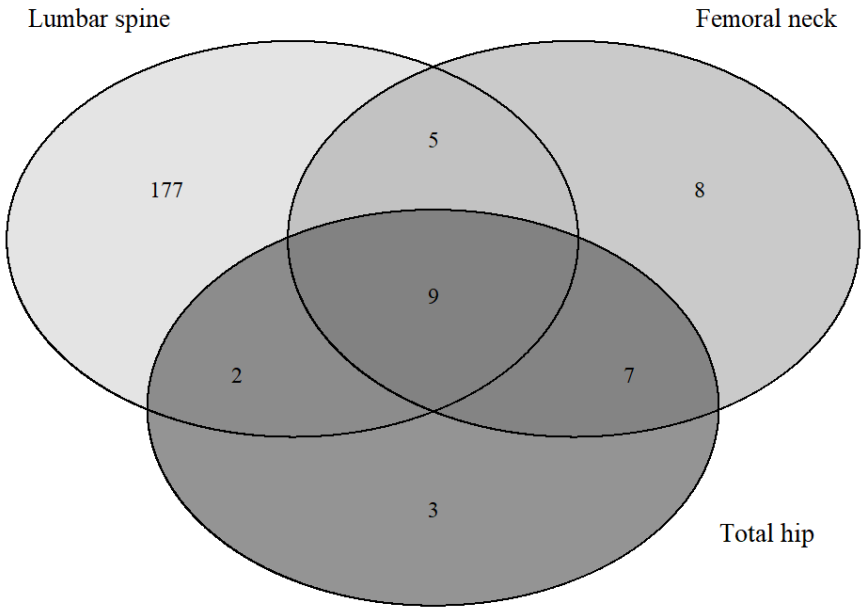

Figure 2: Causes of high bone mass (n=215)

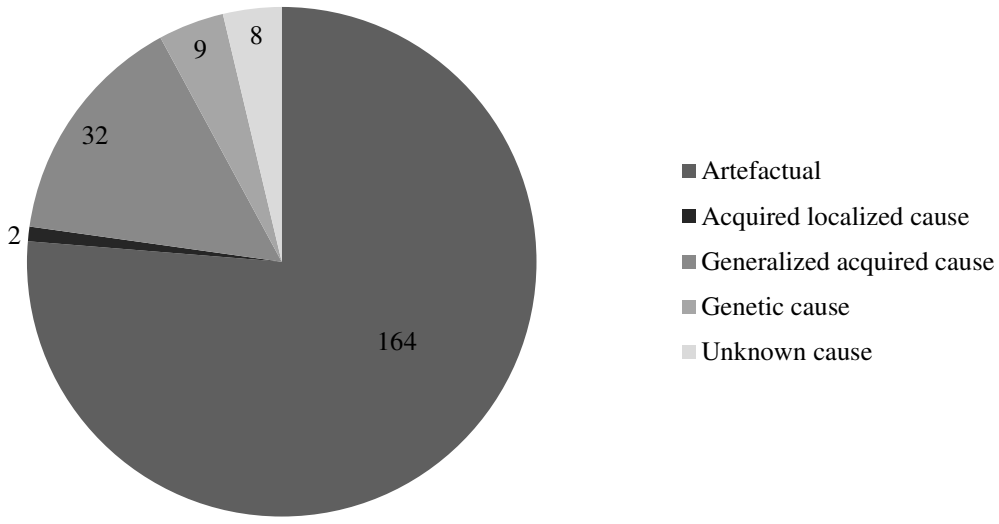

Table 1: Patients' socio-demographic and disease characteristics

Characteristics	**N=211**
Women	119 (56)
Age, years	63.9 (15.5)
Age groups	
- <40	15 (7)
- 40-59.9	58 (28)
- 60-80	110 (52)
- >80	28 (13)
Body Mass Index, kg/m²	
- BMI < 20 kg/m²	8 (4)
- 20 ≤ BMI < 25kg/m²	42 (20)
- 25 ≤ BMI < 30 kg/m²	70 (33)
- BMI ≥ 30 kg/m²	87 (41)
- NC	4 (2)
Cause of referral	
- Post-menopausal osteoporosis	59 (28)
- Male osteoporosis	35 (17)
- Glucocorticoids-induced osteoporosis	31 (15)
- Kidney transplantation	14 (6)
- Liver transplantation	11 (5)
- Other	42 (20)
- Unknown	19 (9)

Values are expressed as mean (standard deviation) or numbers (percentage).

Table 2: Description of genetic causes

Genetic cause	Gender	Age (years)	BMI (kg/m^2)	Z-score	T-score
Osteopetrosis Carbonic anhydrase II deficiency syndrome	M	34	33.1	FN: 4.0 TH: 3.4 LS: 5.4	FN: 3.7 TH: 3.3 LS: 5.4
Steinert's disease	F	45	33.8	FN: 2.2 TH: Uk LS: 4.6	FN: 1.7 TH: Uk LS: 4.3
	F	58	26.8	FN: 2.8 TH: Uk LS: 4.7	FN: 2.0 TH: Uk LS: 4.1
	M	59	29.4	FN: 1.6 TH: Uk LS: 4.1	FN: 0.8 TH: Uk LS: 3.5
Lipodystrophic syndrome	F	77	27.5	FN: 3.0 TH: Uk LS: 5.2	FN: 0.3 TH: Uk LS: 2.5
	F	47	26.2	FN: 2.4 TH: 1.5 LS: 4.1	FN: 1.8 TH: 1.5 LS: 3.8
Hypoparathyroidism GATA 3 mutation	F	43	29.3	FN: 4.2 TH: 3.1 LS: 4.9	FN: 3.6 TH: 2.9 LS: 4.6
Type 1 pseudohypoparathyroidism	F	46	37.2	FN: 1.6 TH: Uk LS: 4.1	FN: 1.2 TH: Uk LS: 3.8
X-linked hypophosphatemia	F	51	30.3	FN: 2.0 TH: Uk LS: 6.4	FN: 1.1 TH: Uk LS: 6.0

M: Male; F: Female; FN: Femoral Neck; TH: Total Hip; LS: Lumbar Spine; Uk: Unknown.

Table 3: Characteristics of patients with unknown cause

Gender	Age (years)	BMI (kg/m^2)	T-score	Z-score	Disease
F	19	16.1	FN: Uk TH: Uk LS: Uk	FN: 4.4 TH: 2.9 LS: 2.4	- Anorexia nervosa - Rheumatoid arthritis
F	43	20.2	FN: 0.7 TH: 2.1 LS: 4.0	FN: 1.2 TH: 2.3 LS: 4.2	- Polyepiphyseal necrosis of undetermined aetiology - Post-Tobacco pulmonary emphysema
F	68	35.1	FN: 1.2 TH: 2.1 LS: 5.3	FN: 2.9 TH: 3.4 LS: 6.0	- Hepatic steatosis with biliary tract abnormality - Hypothyroidism - undifferentiated arthritis
F	51	20.6	FN: 0.0 TH: 0.0 LS: 3.0	FN : 0.9 TH : 0.4 LS : 3.4	- Primary biliary cirrhosis - Post-Hepatic Transplant x2 - Diabetes on pancreatitis (Balthazar E) after transplantation
M	58	28.7	FN: -0.3 TH: 1.0 LS: 3.2	FN: 0.7 TH: 1.5 LS: 3.8	- Post-hepatic transplantation, taking mycophenolate mofetil and carbamazepine - Alcoholic Cirrhosis - Genetic haemochromatosis - Type 2 diabetes
M	75	30.9	FN: 4.2 TH: Uk LS: 5.8	FN: 2.1 TH: Uk LS: 6.8	- NASH Cirrhosis - Ischaemic heart disease - Mixed hypogonadism (post-PVA cranial hematoma, pituitary lesion) without treatment

					- Post-traumatic epilepsy, taking levetiracetam.
M	19	25.5	FN: Uk TH: Uk LS: Uk	FN: 2.8 TH: 1.6 LS: 1.7	- OTC deficit (ornithine transcarbamylase)
M	30	22.8	FN: 6.9 TH: 7.2 LS: 6.4	FN: 7.1 HT: 7.3 LS: 6.4	- Suspicion of osteopetrosis with no mutation found (Supplementary figure 14)

M: Male; F: Female; FN: Femoral Neck; TH: Total Hip; LS: Lumbar Spine; Uk: Unknown.