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# Changes in bone mineral density after allogenic stem cell transplantation

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**ABSTRACT**

**Objective:** Osteoporosis is a complication after allogenic stem cell transplantation (alloSCT). The purpose of this study was to assess changes in bone mineral density (BMD) 6 months and 3 years after alloSCT, as well as predictors of bone loss.

**Methods:** A longitudinal, prospective, single-center study was conducted at Lille University Hospital between 2005 and 2016. Clinical, biological, radiologic (thoracic and lumbar spine) and densitometric (DXA) assessments were carried out at baseline (pre-transplant), 6 months and 3 years. Patients with myeloma were not included.

**Results:** 258 patients were included (144 men). 60.1% of them had leukemia and 65.8% of them, acute myeloid leukemia. At baseline, 6 months and 3 years, DXA-confirmed that osteoporosis was observed in 17%, 22.8% and 17.5% of the patients, respectively, mainly at the femoral neck. At baseline, 6 months and 3 years, 9 (8.5%), 53 (21.5%) and 38 (16.7%) patients, respectively, were receiving anti-osteoporotic treatment.
From baseline to 6-month follow-up, BMD decreased significantly ($p<0.001$) at the lumbar spine (-36 [95%CI; -51 to -20] mg/cm² of hydroxyapatite), femoral neck (-43 [95%CI; -57 to -29] mg/cm² of hydroxyapatite) and total hip (-53 [95%CI; -68 to -39] mg/cm² of hydroxyapatite). From 6-month to 3-year follow-up, a significant increase in BMD was observed at the lumbar spine only (+31 [95%CI; 20 to 42] mg/cm² of hydroxyapatite, $p<0.001$). At all 3 sites, changes in BMD did not differ between patients treated or untreated by anti-osteoporotic treatment from 6-month to 3 year follow-up. Incident fractures were found in 4.1% and 5.7% of the patients at 6 months and 3 years, respectively. Between baseline and 6 months, bone loss at all 3 sites was associated with corticosteroid intake. At the total hip, 23.3% of the decrease in BMD from baseline to 6 months was due to an active hematological disease ($p<0.05$), a bone marrow stem cells ($p<0.01$) and a corticosteroid intake ($p<0.01$).

**Conclusion:** Our study found evidence of bone fragility in alloSCT patients. Low BMD persisted at the hip 3 years after transplantation due to slower improvement at this site.

**KEYWORDS:** osteoporosis, allogenic stem cells transplantation, fracture, bone mineral density.

## 1. Introduction

The number of allogenic stem cell transplantations (alloSCT) is increasing every year. In 2020, 1878 alloSCT patients [1] were registered in France. Improved survival rate among alloSCT patients has led to the observation that these patients may be prone to late rheumatologic complications, such as osteonecrosis and osteoporosis.

In addition to the classical risk factors of osteoporosis (menopause, malnutrition[2]…), alloSCT patients exhibit a number of other risk factors associated with osteoporosis, including chemotherapy[3], radiotherapy, history of autologous hematopoietic stem cells[4–6], secondary hypogonadism[7], corticosteroids therapy and immunosuppressive therapy[8] in patients exhibiting a graft-versus-host (GvH) reaction.

Cohen and al.[9] found that more bone loss occurred after solid organ transplantations than after SCT, with the most bone loss occurring after lung transplantations (57-73% osteoporosis and 42% fractures), and the least after SCT (4-15% osteoporosis and 5% fractures). At Lille University Hospital (LUH), we conducted several osteoporosis studies involving patients who had undergone transplantation (e.g., kidney or liver [10,11]). One of our key findings is that bone loss is higher in the first year after transplantation.

Recommendations for follow-up after hematopoietic cell transplantation were made by expert groups[12] and included active exercise, calcium and vitamin D supplementation, and bone mineral density (BMD) screening using dual photon densitometry a year after transplantation.

The International Osteoporosis Foundation Committee of the Scientific Advisor Group on Cancer and Bone Disease[13] recommends measuring BMD before SCT, at 3 months after SCT for patients who received no anti-osteoporosis treatment, and at one year after SCT for those who did. If a T-score <-1.5 standard deviations (SD) is observed at any one site, treatment should be considered and zoledronic acid is the first treatment of choice. Patients on prolonged corticosteroid therapy should be treated, regardless of the T-score.

Several studies have been carried out[5,14,1] but need to be completed with larger populations, thorough bone assessment and long term follow-up.

The main objective of this study was to assess the changes in bone mineral density (BMD) at 6 months and 3 years after alloSCT. The secondary objective was to identify predictors of bone fragility before and after transplantation.

## 2. Methods

We conducted a prospective, single-center study at LUH, involving a cohort of patients who had undergone alloSCT between January 2005 and December 2016.

All of the patients included in the study gave their consent before inclusion. The study was approved by the CNIL (*Commission Nationale de l'Informatique et des Libertés*).

All of the patients underwent treatment with one or more courses of chemotherapy – and in some cases with corticosteroids, depending on protocols– until an alloSCT was indicated. When a potential donor of stem cells (from bone marrow, peripheral blood stem cells or placenta blood) was found,

the patients received a conditioning regimen – myeloablative (with, sometimes, total body irradiation (TBI)) or not – before undergoing alloSCT. Immunosuppressive treatment (corticosteroids, cyclosporine, mycophenolate mofetil (MMF), mycophenolate sodium, sirolimus or tacrolimus) was introduced after the transplantation and administered in progressively decreasing doses.

The patients underwent 3 rheumatologic assessments by the same rheumatologist: at baseline (before alloSCT, V0), at 6 months (V1) and at 3 years (V2) after alloSCT. All of the patients were summoned for the V0 pre-transplant assessment, but some of them underwent alloSCT soon after hematological diagnosis or indication. Due to lack of time, some of the patients did not undergo a rheumatologic assessment before undergoing alloSCT and had their first assessment 6 months after alloSCT.

We included patients who were at least 18 years old, and had undergone at least two rheumatologic assessments. BMD must have been evaluated at LUH using dual-energy X-ray absorptiometry (DXA). Patients with multiple myeloma were excluded. When the patients underwent several alloSCTs, only the first was considered.

### 2.1 Collection of data

#### 2.1.1 First assessment

We collected data on patients' demographic characteristics, including gender, age and body mass index (BMI). We also collected data on the following osteoporosis risk factors:

- Smoking history;
- Alcohol consumption;
- History of chronic kidney failure, thyroid disease and, for women, menopausal status and early menopause (before 40 years old);
- Significant glucocorticoid therapy (more than 7.5 mg per day for at least 3 months);
- History of osteoporosis or femoral neck fracture in patients and relatives;
- Personal history of non-traumatic fractures;
- Estimation of daily intake of dietary calcium using the Fardellone self-questionnaire[16].

We also recorded the hematologic disease and type of therapy (corticosteroids or immunosuppressive therapy).

Patients underwent biological blood and urine tests, including:

- Serum levels of calcium, phosphorus, 25(OH)vitaminD3, parathyroid hormone, 24-hour urinary calcium and kidney function,
- Markers of bone remodeling, with markers of bone resorption (cross laps) and bone formation (bone alkaline phosphatase and osteocalcin). Osteocalcin was measured by radioimmunoassay (Cis-Bio International, Gif-sur-Yvette; normal values: 10.4-45.6 ng/ml). Bone alkaline phosphatases were measured using a human-specific immunoradiometric method (Hybritech, Inc., Dan Diego, CA, USA; normal values: 2.9-14.5 µg/l). Serum CTX was measured by immuno-enzyme assay (ELISA) (serum crossLaps One Step, Osteometer Biotech, Herlev; normal values: 232-5115 pmol/l);
- Endocrine assessment (thyroid, gonadotropin and somatotropin).

Bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry. Measurements were made at the lumbar spine, total hip and femoral neck using a HOLOGIC machine (HOLOGIC Discovery, HOLOGIC Inc., Waltham, MA, USA). Osteoporosis was defined as a T-score ≤-2.5 standard deviations (SD) at at least at one site, and osteopenia as a T-score between -1 and -2.5 SD[17]. Some of our patients were well below the age of 50 years, which theoretically requires the use of the Z-scores instead of T-scores. However, for the purpose of clarity, we have presented the results for the entire population using T-scores, assuming that in young subjects, by definition, the Z-score is equal to the T-score.

Plain anteroposterior and lateral radiographs of the thoraco-lumbar spine were performed for the purpose of diagnosing vertebral fractures. All radiographs were interpreted by both a rheumatologist and a radiologist from the Department of Osteo-Articular Imaging. Vertebral fractures were defined according to the Genant classification [18] as a loss in vertebral body height of at least 20-25%. In case of discrepancies, the diagnosis of vertebral fracture was obtained by consensus.

On completion of this thorough assessment, treatment was started. The choice of treatment was determined based on French osteoporosis recommendations[19,20], BMD results, the presence of vertebral fractures or a past history of non-vertebral fractures, and the presence of osteoporosis-related risk factors. The proposed drugs were bisphosphonates (alendronate, risedronate and zoledronic acid), or teriparatide, depending on the situation and on the investigator. There was no pre-established treatment protocol.

#### 2.1.2 Second and third assessment

At each visit, we checked for additional osteoporosis risk factors, immunosuppressive treatments and duration of glucocorticoid therapy, and made sure that the bone treatments proposed at the previous assessment were well established and correctly followed by interviewing patients. A thorough biological assessment (see above) was performed at the first assessment (V0, or V1 for those who were not evaluated at baseline) and was not repeated thereafter, except for serum levels of calcium, phosphorus, 25(OH)D3, parathyroid hormone and kidney function. At the end of the visits, an adapted form of treatment was proposed.

### 2.2 Statistical analysis

Categorical variables are expressed as numbers (percentage). Continuous variables are expressed as means ± standard deviation (SD) in the case of normal distributions, or medians [interquartile range] otherwise. The normality of distributions was assessed using histograms and the Shapiro Wilk test.

Baseline characteristics were described according to whether or not the bone remodeling evaluation was conducted at the baseline visit (before alloSCT) and differences were quantified by calculating the absolute standardized difference (ASD); an ASD>20% was interpreted as a meaningful difference.

Variations in biological data between baseline and the first-follow-up visit (6 months) were analyzed using linear mixed models – an unstructured covariance pattern model to account for the correlation between repeated measures – with visits as the fixed effect and taking all available measures into account. We also used similar linear mixed models to assess changes in BMD at each site (total hip, femoral neck and lumbar spine) from baseline (pre-alloSCT) to follow-up assessment (6 months and 3 years). Post-hoc comparisons between baseline and 6-month visits, and between 6-month and 3-year

visits, were made using linear contrasts. The normality of model residuals was checked using quantile-quantile (Q-Q) plots. A sensitivity analysis was performed on the subgroups of patients assessed at all 3 rheumatologic visits.

We assessed the factors associated with bone fragility by looking at the association between BMD changes from baseline to 6 months for each sites with patients' characteristics at baseline and during 6-month follow-up period. Bivariate analyses were firstly done using linear regression models for continuous factors, and analysis of covariance (ANCOVA) for categorical factors, adjusted for baseline BMD values. Factors found to be associated in bivariate analyses, at $p<0.10$, were introduced in multivariable linear regression model adjusted for baseline BMD values. We also reported the associations of patients' characteristics (at baseline and during 6 months follow-up period) with the change in BMD from 6 months to 3 years at the lumbar spine.

We compared the changes in BMD at each site from 6-month to 3-year follow-up in patients who were receiving anti-osteoporotic treatment at 6 months and those who were not, using analysis of covariance (ANCOVA) adjusted for 6-month BMD values.

Statistical analysis was conducted at the two-tailed $\alpha$-level of 0.05. Data were analyzed using the SAS software version 9.4 (SAS Institute, Cary, NC).

## 3. RESULTS

### 3.1 Descriptive analysis

Between January 2005 and December 2016, 996 patients underwent alloSCT. Of those, 258 with at least two rheumatologic visits were included in the present study (Figure 1). One hundred and six (41.1%), 246 (95.3%) and 228 (88.4%) were evaluated at baseline, 6-month and 3-year follow-up, respectively, but only 64 of them (24.8%) attended all 3 visits. The first rheumatologic assessment was performed on 106 patients (41.1%) at baseline and on 152 patients (58.9%) at 6 months. 228 patients were evaluated at 3 years after alloSCT. Of the 30 patients who did not attend the 3-year follow-up visit, after attending the 6-month visit, 14 died. The median follow-up time for the first visit (V1) and the second (V2) were 6.0 [IQR (interquartile range), 6 to 7] months and 38.0 [IQR, 31 to 44] months after alloSCT, respectively.

### 3.2 First assessment

#### 3.2.1 Patients' characteristics

Table 1 shows the main characteristics of the patients at the time of alloSCT. Overall, 114 (55.8%) were men, with a mean age of 47.8±13.8 years. Mean BMI was 24.2±4.8 kg/m². We combined the 155 patients with leukemia (AML + ALL + CLL) (60.1%), the 44 patients with lymphoma (NHL + HL + TL) (17%) and the 59 patients with other hematological diseases (22.9%). Before undergoing alloSCT, 153 patients (59.8%) recovered completely and 20 patients (7.8%) were stable. Most of the patients received bone marrow stem cells (59.3%) and a myeloablative conditioning regimen (53.5%). Only 8 patients (3.1%) received placenta stem cells. 104 patients (40.3%) received corticosteroid treatment with their chemotherapy before alloSCT.

Baseline characteristics were described according to whether or not the first evaluation was conducted at the baseline visit (before alloSCT) in Table S1 [See the supplementary material

associated with this article online]. We observed some meaningful differences, for example in BMI (ASD 22.0%), menopause (ASD 52.9%), familial history of femur fracture (ADS 22.1%), statut before alloSCT (ASD 25%), myeloablative conditioning regimen (ASD 38.8%), total body irradiation (ASD 34.7%), and mycophenolate sodium treatment (ASD 25.8%).

**3.2.2 Biological data at baseline**

Mean serum calcium (92.8±4.4 mg/L; normal values 85-105 mg/L), mean serum phosphate (36.8±6.8 mg/L; normal values 25-45 mg/mL) and mean blood creatinine (8.6±2.2 mg/L; normal values 5-10 mg/mL) were normal. 98 (95.1%) patients had vitamin D deficiency (25(OH)D3 below 30 ng/mL), with a mean level at 15.5±7.9 ng/mL (normal values 30-60 ng/mL), and PTH levels were slightly higher than normal (53.7±27.4 pg/mL; normal values 10-50 pg/mL). Bone resorption marker levels were high, with a high mean serum CTX at 5508±3656 pmol/L. Bone formation markers levels were in normal range, with mean osteocalcin at 25.4±15.8 ng/mL and mean ALP at 15.5±8 mg/L. The endocrine markers were in the normal range. In men, mean serum testosterone was 4.6±2.1 ng/mL (normal values 2,4-8,7 ng/mL). Only 4 men had secondary hypogonadism at baseline.

**3.2.3 Bone fragility at baseline**

Of the 258 patients, 35 (13.6%) reported a past history of low-trauma fragility fracture. We observed 4 fractures of the upper extremity of the femur, 2 symptomatic vertebral fractures, 10 wrist fractures, 1 humerus fracture, 3 rib fractures, 1 pelvic fracture, 8 ankle fractures and 6 others fractures (knee, arm, and clavicle).

Of the 106 patients who underwent a spine X-ray at baseline, 9 had at least one vertebral fracture.

Of the 160 patients at baseline, 17 of them had a history of fragility fracture. Among those with a T-score <-2.5 SD at the total hip, none had a history of fragility fracture. But among those with a T-score <-2.5 SD at the femoral neck or lumbar spine, 2 had a history of fragility fracture.

52 patients had osteopenia (49.1%) and 18 had osteoporosis (17%) (Table 2). Of the 9 patients with vertebral fractures identified by X-ray, 3 had osteoporosis.

**3.2.4 Treatments at baseline**

Of the 106 patients seen at baseline, 95 (89.6%) received a prescription for vitamin D supplementation and 16 (15.1%) for calcium supplementation. 9 patients (8.5%) received an anti-osteoporotic treatment (alendronate (n=5), risedronate (n=2), zoledronic acid and another bisphosphonate (n=2)). The others osteoporotic patients received vitamin D supplementation before initiating treatment.

**3.3 Follow-up rheumatologic assessment**

***3.3.1 Fracture data***

Between baseline and 6-month follow-up, 10 patients (4.1%) were diagnosed with a new fracture, and 5 of them had at least one radiological and asymptomatic vertebral fracture. Others fractures

included a wrist, a pelvic and a knee fracture. Among the patients included at the 6-month follow-up, spine X-ray images revealed that 11 had vertebral fractures, but it was impossible to know when they occurred.

Between 6-month and 3-year follow-up visits, 13 patients (5.7%) had a new fracture, and 7 of them had at least one radiological and asymptomatic vertebral fracture. Other fractures included a knee, a clavicle, a humerus and a wrist fracture.

#### *3.3.2 Biological data*

At the 6-month follow-up visit, the mean levels of 25(OH)vitamin D was 23.2±17.7 ng/mL, which was significantly higher than at baseline ($p \leq 0.001$). Bone markers were assessed in all of the 152 patients who were first included at the 6-month visit. In those patients, bone resorption marker levels were not higher compared with the other patients assessed at baseline, the mean serum CTX was 6489±3199 pmol/L ($p=0.08$). Osteocalcin levels (33.5±21.3 ng/mL) were significantly higher than at baseline ($p<0.05$) and ALP levels were in the normal range (17.7±11.1 mg/L) with no significant difference between baseline and 6-month follow-up.

At 3–year follow-up, the mean level of 25(OH)vitamin D was 27±17.2 ng/mL, which was higher than at 6-month follow-up. Mean serum calcium (94.8±4.4 mg/L) and serum phosphate (32.6±6.9 mg/L) levels were in the normal range.

#### *3.3.3 DXA assessment*

At 6-month follow-up, 125 patients had osteopenia (50.8%) and 56 osteoporosis (22.8%). Low BMD was still mainly found at the femoral neck.

For the 91 patients who were receiving corticosteroids at 6 months, mean T-scores at the total hip, femoral neck and lumbar spine were -0.9±1.2 SD, -1.4±1.3 SD and -0.7±1.8 SD, respectively.

At 3-year follow-up, 119 patients had osteopenia (52.2%) and 40 had osteoporosis (17.5%).

For the 50 patients who were receiving corticosteroids at 3 years, mean T-scores at the total hip, femoral neck and lumbar spine was -1.1±1.0 SD, -1.6±1.0 SD and -1.0±1.3 SD, respectively.

#### 3.3.4 Treatments

During follow-up, 168 patients (65.1%) developed a graft-versus-host (GvH) reaction. The reaction was acute in 122 patients, and chronic in 112 patients. Most of reactions were dermatological (50% of cases). For immunosuppressive purposes, 96.9% of the patients were treated by ciclosporin for an average duration of 11.3±8.1 months, and 77.1% for a duration of more than 6 months. The median duration of corticosteroid treatment was 9.0 [IQR, 5 to 16] months. Corticosteroid therapy was administered at a dose of 1 or 2 mg/kg/day for 53.9% of patients. In 43% of the patients, the duration of treatment exceeded 3 months. The average dose at the beginning of treatment was 70.7±16.2 mg per day.

At 6-month follow-up, 207 patients (84.1%) were receiving vitamin D supplementation, and 44 patients (18%) were receiving calcium supplementation. Of the 56 osteoporotic patients, 53 (94.6%) were receiving anti-osteoporotic treatment (alendronate (n=31), risedronate (n=10), zoledronic acid

(n=9), other bisphosphonates (n=2) and strontium ranelate (n=1)). Two patients who started alendronate at baseline switched to risedronate because of poor tolerance.

At 3-year follow-up, 196 patients (86.7%) were receiving vitamin D supplementation and 28 patients (12.3%) were receiving calcium supplementation. Of the 40 osteoporotic patients, 38 (95%) were receiving anti-osteoporotic treatment (alendronate (n=13), risedronate (n=7), zoledronic acid (n=14), denosumab (n=1), pamidronate (n=1), strontium ranelate (n=1) and teriparatide (n=1)). Thirteen patients who had been receiving anti-osteoporosis treatment since the 6-month follow-up visit changed their treatment because of poor tolerance or inefficiency.

### 3.4 Changes in BMD

As shown in Figure 2, from baseline to follow-up, changes in BMD were observed at the 3 sites assessed for comparison purposes (total hip, femoral neck and lumbar spine) ($p<0.001$), and regardless of whether patients were receiving anti-osteoporosis treatment or not. From baseline to 6-month follow-up, BMD decreased significantly ($p<0.001$) with a mean decrease at the total hip, femoral neck and lumbar spine of 53 [95%CI; 39 to 68] mg/cm² of hydroxyapatite, 43 [95%CI; 29 to 57] mg/cm² of hydroxyapatite and 36 [95%CI; 20 to 51] mg/cm² of hydroxyapatite, respectively. From 6-month to 3-year follow-up, a significant increase in BMD was found at the lumbar spine only, with a mean increase of 31 [95%CI; 20 to 42] mg/cm² of hydroxyapatite ($p<0.001$). For other sites, no significant changes were found. At the total hip, BMD remained unchanged at 5 [95%CI; -6 to 15] mg/cm² of hydroxyapatite. In the same manner, at femoral neck, BMD did not change (-2 [95%CI;-12 to 8] mg/cm² of hydroxyapatite).

In the subgroup of 64 patients who underwent all 3 rheumatologic assessments, the same changes were observed, except that a significant increase in BMD was observed at the total hip from 6-month to 3-year follow-up, with a mean increase of 28 [95%CI; 10 to 46] mg/cm² of hydroxyapatite without being completely compensated for when compared to baseline value ($p<0.01$).

We were unable to compare changes in BMD from baseline to 6-month follow-up in patients who received anti-osteoporotic treatment and those who had not, because only 8 patients were treated. However, from 6-month to 3-year follow-up, we found no difference in changes in BMD between untreated patients and the 53 treated patients at the 3 sites. In the treated patients, the mean changes in BMD at the total hip, femoral neck and lumbar spine were statistically non-significant with +2±9 mg/cm² of hydroxyapatite, +2±9 mg/cm² of hydroxyapatite and +6±7 mg/cm² of hydroxyapatite, and in the untreated patients 0±8 mg/cm² of hydroxyapatite, -1±7 mg/cm² of hydroxyapatite and +3±10 mg/cm² of hydroxyapatite, respectively.

#### 3.4.1 Factors associated with changes in BMD

##### 3.4.1.1 From baseline to 6-month follow-up

We assessed the factors associated with early changes in BMD in the 94 patients who underwent rheumatologic assessments at both baseline and 6-month follow-up.

In bivariate analysis, progressive disease ($R^2=0.07$, $p<0.05$), bone marrow stem cells ($R^2=0.06$, $p<0.05$), MMF treatment ($R^2=0.04$, $p<0.1$) and the introduction of corticosteroids between baseline and 6-month follow-up ($R^2=0.05$, $p<0.05$) were found to be significantly associated with total hip bone loss (Table S2). In multivariate analysis (table 3), progressive disease (partial $R^2=0.07$, $p<0.05$);

bone marrow stem cells (partial $R^2$=0.09, p<0.01) and corticosteroids between baseline and 6-month follow-up (partial $R^2$=0.07, p<0.01) were significantly associated with total hip bone loss.

BMI less or equal than 21kg/m² ($R^2$=0.13, p<0.05), bone marrow stem cells ($R^2$=0.16, p<0.05), myeloablative conditioning regimen ($R^2$=0.11, p<0.1), corticosteroids introduced between baseline and 6-month follow-up ($R^2$=0.14, p<0.05) and MMF treatment ($R^2$=0.15, p<0.05) were associated with a negative change in BMD at the femoral neck (Table S2). These results were confirmed in multivariate analysis (table 3) for BMI less or equal than 21kg/m² (partial $R^2$=0.04, p<0.05); bone marrow stem cells (partial $R^2$=0.06, p<0.05); corticosteroids between baseline and 6-month follow-up (partial $R^2$=0.05, p<0.05) and MMF treatment (partial $R^2$=0.12, p<0.001)

Myeloablative conditioning regimen ($R^2$=0.11, p<0.05), corticosteroid treatment during more than 3 months ($R^2$=0.09, p<0.1), high serum ALP ($R^2$=0.1, p<0.1), high serum CTX at baseline ($R^2$=0.11, p<0.05), and corticosteroids introduced between baseline and 6 months ($R^2$=0.14, p<0.01) were associated with a negative change in BMD at the lumbar spine (Table S2). These results were confirmed in multivariate analysis (table 3) for corticosteroids introduced between baseline and 6 months (partial $R^2$=0.04, p<0.05) and myeloablative conditioning regimen (partial $R^2$=0.04, p<0.05).

#### 3.4.1.2 From 6-month to 3-year follow-up

Since there were no significant changes in BMD at the femoral neck and total hip, we only investigated the impact of factors on the lumbar spine. In bivariate analysis, of the 216 patients who underwent rheumatologic assessments at 6-month and 3-year follow-up, absence of chronic GvH ($R^2$=0.16, p<0.05), male individuals ($R^2$=0.22, p<0.001), BMI better than 21 kg/m² at baseline ($R^2$=0.17, p<0.05), MMF treatment ($R^2$=0.16, p<0.1) and myeloablative conditioning regimen ($R^2$=0.17, p<0.05) were found to have a significant positive impact (Table S3).

Next, we analyzed independent association of positive impact by multivariate analysis (Table S3). Positive impact was independently associated with male individuals (partial $R^2$=0.07, p<0.001), BMI better than 21kg/m² at baseline (partial $R^2$=0.03, p<0.01), myeloablative conditioning regimen (partial $R^2$=0.02, p<0.05) and the absence of MMF treatment (partial $R^2$=0.02, p<0.05).

## 4. Discussion

We were able to demonstrate that bone loss occurred after alloSCT, predominantly at the femoral neck. Between baseline and 6-month follow-up, we found significant decreases in BMD at the lumbar spine (-36 [95%CI; -51 to -20] mg/cm² of hydroxyapatite), femoral neck (-43 [95%CI; -57 to -29] mg/cm² of hydroxyapatite) and total hip (-53 [95%CI; -68 to -39] mg/cm² of hydroxyapatite) (p<0.001). Between 6-month and 3-year follow-up, a significant increase in BMD was found at the lumbar spine only (+31 [95%CI; 20 to 42] mg/cm² of hydroxyapatite, p<0.001), permitting a return to baseline BMD value. Other studies have described a progressive recovery, first at the lumbar spine and thereafter at the femoral neck. These findings are consistent with ours, as we did not find a recovery in femoral neck BMD at 3-year follow-up. Buchs and al.[15] reported significant decreases in femoral neck BMD (-4.1±0.7%) and whole body BMD (-1.5±0.4%) (p<0.001), but not lumbar spine BMD, between the pre-transplant period and 6-months follow-up. At 12-month follow-up, only femoral neck BMD was lower than at baseline (-5.6±1.1%, p<0.001). In a study conducted by Anandi and al.[21], in which 148 patients were followed up over a period of 20 years, the authors found that

bone loss stabilized between year 3 and year 5, before gradually improving between year 5 to year 15, without bisphosphonate. In a study conducted by Baumgartner and al.[22], in which patients were followed up every 3 months for 2 years, and then every year, the authors reported that BMD was low the first year, stabilized for 5 years, then increase between year 6 and year 10. Several studies[23] have reported that the bone loss was higher at femoral neck, and that BMD increased first at the lumbar spine and then at the femoral neck. These findings are consistent with ours.

In our study, at baseline, 6 months and 3 years after alloSCT, 17.5%, 22.8% and 17%of the patients, respectively, had osteoporosis and 49.1%, 50.8% and 52.2%of the patients, respectively, had osteopenia. Schulte and al.[14] reported that, at baseline, only 4% of their patients had osteoporosis and 24% had osteopenia. At one-year and two-year follow-up, 5% and 9% of the patients, respectively, had osteoporosis, but the proportions of patients with osteopenia (44% and 40%, respectively) were higher. According to the authors, the difference could be attributed to the young age of their patients (37±10 years). Baumgartner and al.[22] reported results that were more similar to ours : out of 652 patients, 36% had osteopenia and 13.8% had osteoporosis.

In our study, 4.1% of the patients had incident fractures at 6-month follow-up and 5.7% at 3-year follow-up. These findings are consistent with the literature: Anandi and al.[21] reported a fracture rate of 3.37% (in 148 patients), Baumgartner and al.[22] reported a fracture rate of 4.9% (in 652 patients), and Pundole and al.[6] reported a fracture rate of 5%. Only Stern and al.[24] reported a higher fracture rate (10.6% of 105 patients between 4.5- and 36-month follow-up).

In addition to the well know effect of corticosteroid therapy[22,25], the factors influencing the changes in BMD in our study were progressive disease before alloSCT ($p<0.05$) and use of bone marrow stem cells ($p<0.01$), at the total hip; BMI less or equal than 21 kg/m² ($p<0.05$), use of bone marrow stem cells ($p<0.05$) and MMF treatment ($p<0.001$), at the femoral neck and use of myeloablative conditioning regimen ($p<0.05$) at the lumbar spine. Immune reconstitution is longer in bone marrow stem cell patients and GvH is more acute, as are infections. Hospitalizations are therefore longer and patients are more undernourished and bedridden, which may explain the more deleterious effect on bone[26].

Other factors – not found in our study – have been described as associated with bone loss, including autologous SCT at the lumbar spine and femoral neck, reported by Schulte and al.[14], acute GvH at the lumbar spine reported by Yao and al.[25], and vitamin D deficiency, hyperthyroidism before transplantation, cumulative years of immunosuppressant exposure and acute GvH, reported by Baumgartner and al.[22]

In the group of patients who received anti-osteoporotic treatment, we found no changes in BMD attributable to the treatment between 6 months and 3 years after alloSCT. However, the number of patients was low, and we were unable to assess those patients who received treatment between baseline and 6 months after alloSCT, when bone loss was higher. This can be explained by the fact that hematologic care was preferred over rheumatologic care because of the vital prognosis.

According to the literature, bisphosphonates have a positive impact on changes in BMD. Tauchmanova and al.[27] investigated the effect of risedronate (5 mg per day for 12 months) on BMD in 34 patients with T-score ≤-1.5 SD at one site, assessed at least 6 months after alloSCT. A significant effect ($p<0.1$) was found at the lumbar spine only, where BMD increased by +4.4±1.6%

after 6 months and +5.9±1.7% after 12 months. Intravenous treatments were investigated using different protocols. In 78 patients, treatment with ibandronate at quarterly dose of 3 mg [28], starting within 45 days of alloSCT, reduced bone loss at the lumbar spine, particularly in patients who received glucocorticoids and tacrolimus, but had no impact at the hip at 6 months and 12 months after alloSCT. In a randomized study involving 116 patients treated with pamidronate at a monthly dose of 90 mg[29], the first perfusion was performed a week before alloSCT, and the following at monthly intervals. At 12 months, BMD was 5.6%, 7.7% and 4.9% higher at the lumbar spine, femoral neck and total hip, respectively, in the patients who were treated compared to those who were not. But at 12 months, in the treatment group, bone loss remained significant at the femoral neck and total hip (-2.8% and -3.5%, respectively, compared to baseline). The effect of a 4 mg dose of zoledronic acid was investigated under different protocols (monthly for 3 months[30]; single dose[31]; 2 months after alloSCT and then every 3 months for 2 years[23]; before alloSCT[32,33]). The treatment was found to have a significant effect in preventing bone loss.

In a Korean study [34], denosumab was administered every 6 months for 12 months and found to improve BMD.

New recommendations published in 2021[13] suggest that DXA should be performed before SCT and 3 months after SCT, when anti osteoporosis treatment is not prescribed. However, we believe that this 3-months interval is too short to highlight a possible decrease in BMD. Indeed, it is important to take into account the smallest change with clinical significance, which in the best case is 30mg/cm$^2$ of hydroxyapatite for DXA.

The strengths of our study include its prospective design, the large number of patients – permitting intra- and inter-individual comparison – and the long follow-up. The main limitations were its single-center design and the recruitment bias, as only patients with 2 rheumatologic assessments were included, which is not representative of the entire alloSCT population. Additionally, due to a short interval of time between the decision to perform alloSCT and the actual transplantation, all patients could not be assessed before alloSCT. There are potential biases arising from missing bone remodeling marker evaluations because of some meaningful differences between patient's characteristics first evaluated before alloSCT or after 6-month follow-up.

Our study showed that bone fragility occurred in pre- and post-alloSCT patients, with a highest decrease occurring in the first months. Bone loss was predominant at the hip, where recovery was slower compared to the lumbar spine. We found that corticosteroid treatment, progressive disease before alloSCT and bone marrow stem cells had a negative impact on bone loss. Collaboration between rheumatologists and hematologists is useful, not only to prevent the occurrence of fracture, but also for the initial assessment of BMD and the assessment of BMD during follow-up.

**Disclosure of interest**

The authors declare that they have no conflicts of interest related to this article.

## Online material. Supplementary data

Supplementary data (Table S1-S3) associated with this article can be found in the online version at …

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**Table 1.** **Patients'characteristics (n=258)**

| Characteristics | Values |
|---|---|
| **Men** | 144 (55.8%) |
| **Age at alloSCT** (years) | 47.8 ± 13.8 |
| **BMI** (kg/m²) | 24.2 ± 4.8 |
| **Osteoporosis risk factor** | |
| Alcohol intake | 4 (1.6%) |
| Smoker | 33 (12.8%) |
| Hyperthyroidism | 3 (1.2%) |
| Menopause | 95 (83.3%) |
| Fracture | 35 (13.6%) |
| Family history of femur fracture | 16 (6.3%) |
| Fardellone Score (mg/d) | 834 ± 418 |
| **Hematological disease** | |
| Leukemia (AML + ALL + CLL) | 155 (60.1%) |
| - Acute myeloid leukemia (AML) | 102 (65.8%) |
| - Acute lymphocytic leukemia (ALL) | 39 (25.2%) |
| - Chronic lymphocytic leukemia (CLL) | 14 (9.0%) |
| Lymphoma (NHL + HL +TL) | 44 (17.0%) |
| - Non-Hodgkin lymphoma (NHL) | 26 (59.1%) |
| - Hodgkin lymphoma (HL) | 12 (27.3%) |
| - T-Cell leukemia (TL) | 6 (13.6%) |
| Others | 59 (22.9%) |
| - Myelodysplastic syndrome (MDS) | 30 (50.8%) |
| - Myeloproliferative disorders (MPD) | 17 (28.8%) |
| - Medullary aplasia | 6 (10.2%) |
| - Chronic myelomonocytic leukemia (CMML) | 4 (6.8%) |
| - Other hematologic diseases | 2 (3.4%) |
| **Hematologics characteristics** | |
| Corticosteroid during chemotherapy | 104 (40.3%) |
| Autologous SCT | 38 (14.7%) |
| Statut before alloSCT | |
| - Complete response / Stable disease | 173 (67.6%) |
| - Progressive disease | 60 (23.4%) |

| | |
|---|---|
| - Partial response | 23 (9.0%) |
| **AlloSCT characteristics** | |
| Type of stem cell | |
| - Bone marrow | 153 (59.3%) |
| - Peripheral blood | 97 (37.6%) |
| - Placenta | 8 (3.1%) |
| HLA identical sibling | 112 (43.4%) |
| Myeloablative conditioning regimen | 136 (53.5%) |
| Total Body Irradiation | 97 (37.7%) |
| Immunosuppressive treatments | |
| - Corticosteroids | 139 (53.9%) |
| - Cyclosporine | 250 (96.9%) |
| - Mycophenolate mofetil | 34 (13.2%) |
| - Mycophenolate sodium | 13 (5.0%) |
| - Sirolimus | 3 (1.2%) |
| - Tacrolimus | 22 (8.5%) |

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

**Table 2**. **Changes in T-score and BMD at baseline, 6 months and 3 years**

| | V0 | | V1 | | V2 | |
|---|---|---|---|---|---|---|
| | **T-score (SD)** | **BMD (g/cm²)** | **T-score** | **BMD** | **T-score** | **BMD** |
| **Total hip** | -0.6±1.1 | 0.93±0.15 | -0.9±1.1 | 0.89±0.15 | -0.7±1.1 | 0.90±0.15 |
| **Femoral neck** | -1.1±1.2 | 0.79±0.14 | -1.3±1.1 | 0.76±0.13 | -1.2±1.1 | 0.75±0.14 |
| **Lumbar spine** | -0.5±1.6 | 1.00±0.17 | -0.8±1.4 | 0.97±0.16 | -0.6±1.2 | 0.99±0.14 |

Values are expressed as mean ± standard deviation.

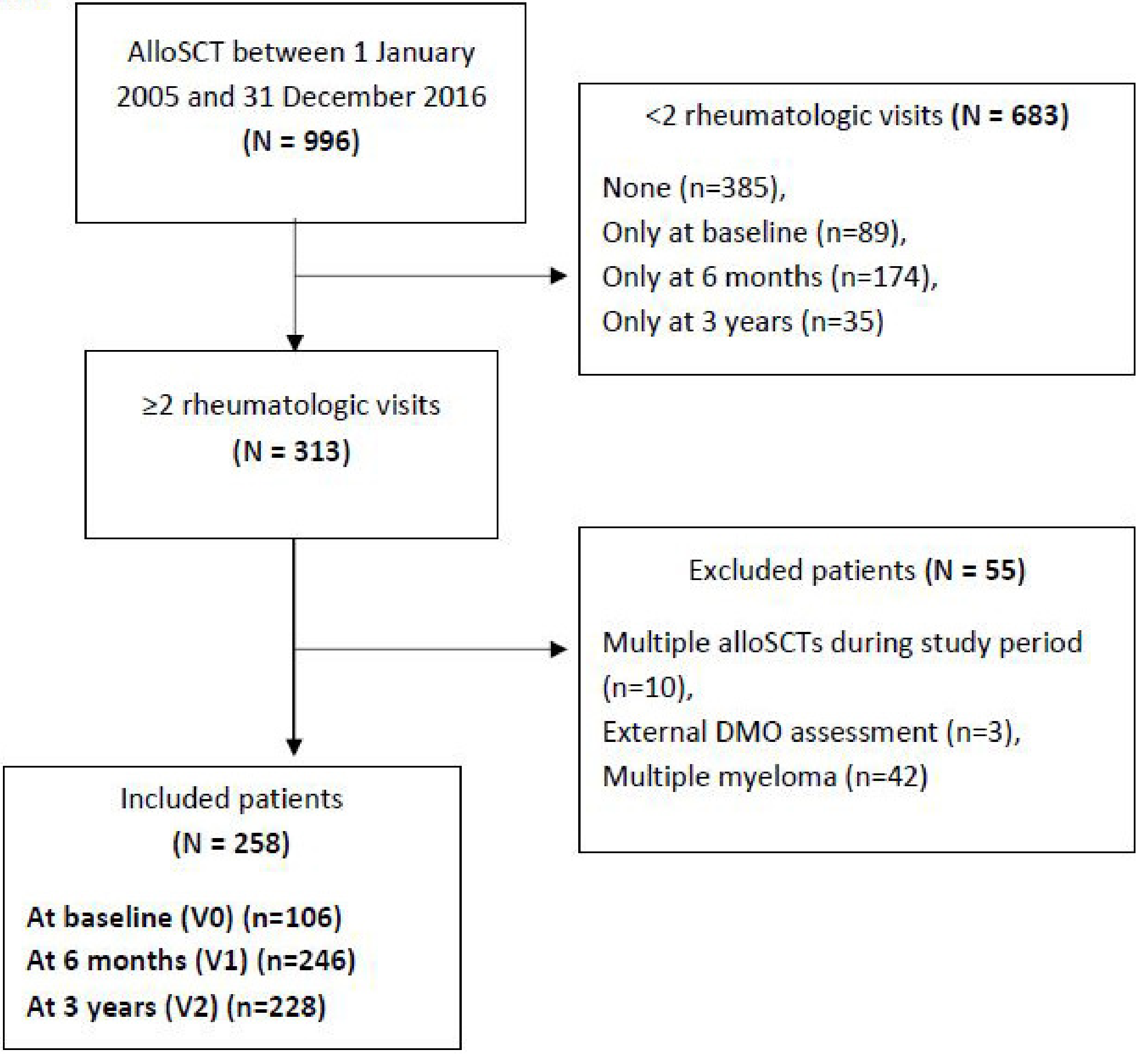
**Table 3: Multivariate analysis for factors associated with changes in BMD from baseline to 6-month follow-up.**

| | β [95%CI] | $R^2$ |
|---|---|---|
| **Model 1 : Total hip (global $R^2$)** | | **0.23**** |
| Statut before alloSCT | | 0.07* |
| Progressive disease | 1.00 (reference) | |
| Complete response / stable disease | 2.97 [0.60 to 5.34] | |
| Partial response | 3.97 [0.73 to 7.21] | |
| Stem cell source | | 0.09** |
| Bone marrow | 1.00 (reference) | |
| Peripheral blood | 3.03 [1.03 to 5.03] | |
| CTC between V0 and V1 | -2.58 [-4.49 to -0.68] | 0.07** |
| MMF | -3.51 [-7.22 to 0.21] | NS |
| **Model 2 : Femoral neck (global $R^2$)** | | **0.34***** |
| BMI<21kg/m² | -2.66 [-5.25 to -0.06] | 0.04* |
| Myeloablative conditioning regimen | -0.89 [-3.18 to 1.41] | NS |
| Stem cell source | | 0.06* |
| Bone marrow | 1.00 (reference) | |
| Peripheral blood | 3.11 [0.76 to 5.46] | |
| CTC between V0 and V1 | -2.62 [-4.72 to -0.51] | 0.05* |
| MMF | -7.69 [-11.77 to -3.61] | 0.12*** |
| **Model 3 : Lumbar spine (global $R^2$)** | | **0.20*** |
| CTC during>3months | 0.12 [-2.72 to 2.96] | NS |
| CTC between V0 and V1 | -2.98 [-5.86 to -0.11] | 0.04* |
| Myeloablative conditioning regimen | -2.15 [-4.24 to -0.05] | 0.04* |
| Serum CTX | -0.33 [-1.47 to 0.82] | NS |
| ALP | -0.26 [-1.58 to 1.06] | NS |

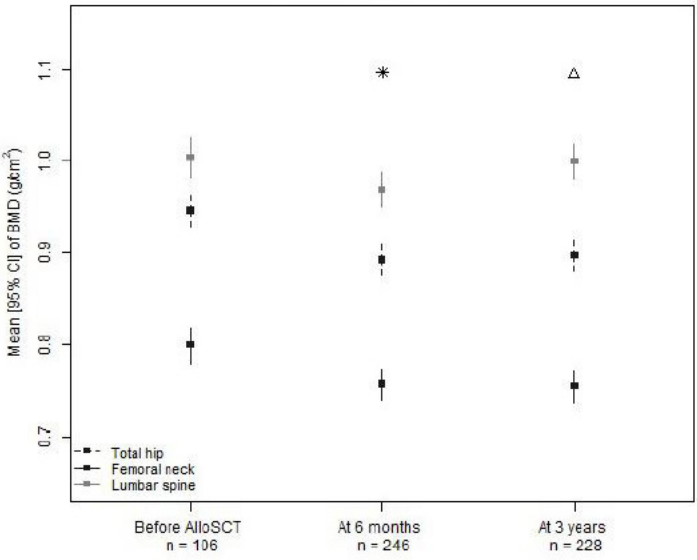
β were calculated per one deviation standard increase for continuous variables.
*P<0.05, **P<0.01, ***P<0.001. NS : non significant.

**Figure 1.** **Flow chart**

**Figure 2.** **Changes in BMD over time in the study population and in the sub-groups of patients who underwent all 3 rheumatologic assessments**


AlloSCT between 1 January 2005 and 31 December 2016 (N = 996)
<2 rheumatologic visits (N = 683)
None (n=385),
Only at baseline (n=89),
Only at 6 months (n=174),
Only at 3 years (n=35)
≥2 rheumatologic visits (N = 313)
Excluded patients (N = 55)
Multiple alloSCTs during study period (n=10),
External DMO assessment (n=3),
Multiple myeloma (n=42)
Included patients (N = 258)
At baseline (V0) (n=106)
At 6 months (V1) (n=246)
At 3 years (V2) (n=228)

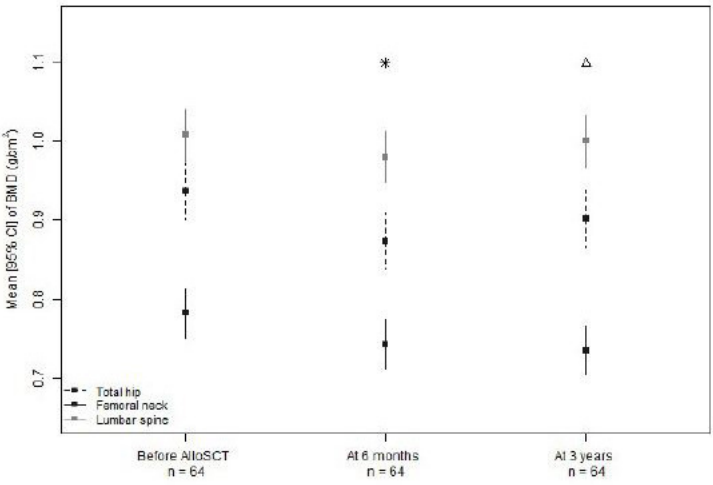
**In the study population**




✳ p<0.001 for comparisons between baseline and 6 months for 3 sites.

△ p=0.37 for comparison between 6 months and 3 years at the total hip.
p=0.70 for comparison between 6 months and 3 years at the femoral neck.
p<0.001 for comparison between 6 months and 3 years at the lumbar spine.

**In patients with all 3 rheumatologic assessments**




✳ p<0.001 for comparisons between baseline and 6 months at the total hip and the femoral neck.
p=0.004 for comparison between baseline and 6 months at the lumbar spine.

△ p=0.003 for comparison between 6 months and 3 years at the total hip.
p=0.42 for comparison between 6 months and 3 years at the femoral neck.
p=0.035 for comparison between 6 months and 3 years at the lumbar spine.