

# Low Bone Mineral Density and High Bone Turnover in Patients With Non-Hodgkin's Lymphoma (NHL) Who Receive Frontline Therapy: Results of a Multicenter Prospective Study

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## Abstract

Chemotherapy associated osteoporosis is a severe problem in patients with malignant diseases as it increases the risk for fractures and deteriorates quality of life. There are very limited data in the literature for the effect of chemotherapy on bone metabolism of adult patients with Non-Hodgkin Lymphoma (NHL). We prospectively evaluated bone remodeling pre- and post-chemotherapy in 61 patients with newly diagnosed NHL. First-line chemotherapy resulted in high bone turnover, which led to increased bone loss and reduced bone mineral density (BMD) of lumbar spine (L1-L4) and femur neck (FN). The reduction of L1-L4 and FN BMD post-chemo was more profound in males and in older patients (>55 years). Patients who received 8 cycles of chemotherapy had a greater reduction of L1-L4 and FN BMD as compared to 6 cycles. The administration of chemotherapy also resulted in a dramatic increase of bone resorption markers (CTX and TRACP-5b), bone formation markers, (bALP and Osteocalcin) and of osteoblast regulator Dickkopf-1. During study period, one patient had a pathological fracture in his right FN.

## Introduction

Survivorship issues for patients with lymphomas, including bone health, are of increasing importance as long-term

outcomes continue to improve with the advances in immune-chemotherapy.<sup>1</sup> Chemotherapy-induced bone loss is a well-established treatment complication in all patients with malignancies and bone mineral density (BMD) reduction has been reported in adult patients with lymphoma post-chemotherapy administration.<sup>2</sup> Osteopenia and osteoporosis is however a common finding also in untreated patients with Non-Hodgkin's lymphoma (NHL).<sup>3,4</sup> The long-term sequelae associated with osteoporosis remains an important issue due to the associated mortality and morbidity. Very few studies have addressed the issue of bone metabolism in the setting of adult lymphoma<sup>5</sup> and it remains currently unclear to what extent the harmful effects on bone in these patients are the effect of the tumor itself or the treatment.<sup>6</sup>

Lymphoma treatment regimens are multi-agent and often followed by autologous stem cell transplant (ASCT) making it even harder to delineate the effect of individual agents on bone metabolism and to identify which agent(s) and to what extent contributes to bone loss. The effect of exogenous glucocorticoids on bone metabolism via increased bone resorption, decreased bone formation, calcium retention and endocrine gonadal dysfunction is well established.<sup>6-10</sup> Alkylating agents can also induce gonadal damage and consequently affect bone metabolism. The association has been demonstrated in breast and prostate cancer patients.<sup>11-13</sup>

Given the absence of robust data linking lymphoma biology or chemotherapy agents to bone loss there is also a lack of formal

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recommendation regarding bone investigations that assess BMD at baseline or prophylactic bone management during and post-treatment administration. More studies, both pre-clinical to assess effects of agents and lymphoma cells on bone biology and clinical trials are required to help distinguish between the chemotherapy effect and the intrinsic effect of lymphoma on bone loss. Development of guidelines that will allow appropriate selection of high-risk patients that will benefit from the use of prophylactic measures is crucial.

The aim of the present study is to assess bone metabolism and bone mineral density in newly diagnosed patients with NHL prior and post-chemotherapy administration to provide some insight on the mechanisms of bone loss in these patients for which long-term sequelae of treatment complications are becoming more relevant with improved outcomes.

## Patients and methods

### Study design

The purpose was to prospectively perform a thorough assessment of bone remodeling in newly diagnosed patients with NHL pre- and post-first-line chemotherapy.

From June 2009 until January 2012, 61 newly diagnosed patients with NHL recruited from three Hematology departments in Athens, Greece entered their study and had completed their chemotherapeutic scheme. Patients with lymphoma bone-involvement or with known osteoporosis receiving medication therapy could not enter the study. Exclusion criteria included previous bone fractures, Creatinine Clearance < 60 ml/min, dental problems that would potentially require interventions putting patients at risk of jaw osteonecrosis, prior bisphosphonate or significant corticosteroid use for other medical reasons, endocrine problems both controlled and uncontrolled (primary or secondary hyperparathyroidism), metabolic bone diseases (ie, Paget disease) and previous radiotherapy to lumbar spine. Patients did not receive vitamin D or calcium supplementation while on study. Data on the pre or post-menopausal status of the female patients was not collected.

Osteopenia and osteoporosis were defined according to the definition of the World Health Organization as a BMD T-score of  $-1.0$  to  $-2.5$  and less than  $-2.5$ , respectively.<sup>14</sup>

The study was conducted after approval by the Ethics Committee/Institutional review board and informed consent was obtained prior to any intervention.

### Bone mineral density and bone remodeling markers

Bone Mineral Density (BMD) of the lumbar spine (L1-L4, antero-posterior view), and Femoral Neck (FN) was measured by dual energy X-ray absorptiometry (DXA) using a Hologic QDR-1000 scanner on day 1 of cycle 1 (baseline) and on day 30 post the last cycle of chemotherapy. The vertebra with the lowest T-score was identified as the lumbar vertebra with the major bone loss and this value was compared prior and post-chemotherapy.

Serum markers of bone remodeling were measured on samples collected on the days of DXA, using ELISA methodology: (i) osteoclast and osteoblast regulators [soluble receptor activator of nuclear factor B ligand (sRANKL), osteoprotegerin (OPG) a soluble decoy receptor of RANKL, osteoblast inhibitor dickkopf-1 (Dkk-1)] (Biomedica Medizinprodukte, Gesellschaft GmbH & Co. KG, Wien, Austria), (ii) bone resorption markers: NTX (Osteomark® NTx Serum, Ostex International, Seattle, WA),

carboxy-terminal cross-linking telopeptide of type I collagen (CTX) (serum CrossLaps®, Immunodiagnostic Systems Ltd, Boldon, Tyne & Wear, UK) and 5b isoenzyme of tartrate-resistant acid phosphatase (TRACP-5b; BoneTRAP®, Immunodiagnostic Systems Ltd., Boldon, Tyne & Wear, UK); (iii) bone formation markers [bone-specific alkaline phosphatase (bALP; Metra® BAP, Quidel Corporation, San Diego, CA, USA), and osteocalcin (OC; N/MID® Osteocalcin, Immunodiagnostic Systems Ltd, Boldon, Tyne & Wear, UK)], according to manufacturer instructions, as previously described<sup>15</sup>; Parathyroid hormone (PTH; Cobas, Roche Diagnostic GmbH, Mannheim, Germany) and 25-hydroxyvitamin D (R&D Systems, Minneapolis, MN) were also measured in the routine laboratories of Alexandra Hospital.

The above bone markers were also evaluated in 44 healthy controls of similar age and gender (26M/18F, median age 55 years, range: 25–91 years). Each control was examined to ensure that there was no evidence of bone disease such as osteoporosis or osteoarthritis (patients with BMD T-score of less than  $-2.5$  were excluded), no receipt of medication that could alter the normal bone turnover during the last 6 months (this cut-off is a potential limitation as bisphosphonates have a longer skeletal half-life), and no evidence of infection or autoimmune disease on the day of sampling. For the assessment of osteoporosis all controls had bone mineral density measurements using DXA in both lumbar spine and femoral neck. Patients were assessed for skeletal-related events (SREs) throughout the period of the study.

### Statistics

Descriptive statistics were used to characterize the baseline variables. Differences between patients-controls and different group of patients were evaluated using the Mann-Whitney test. Differences with p value < 0.05 were considered statistically significant. Differences pre and post-chemotherapy in bone metabolism markers and BMD measurements were evaluated using non-parametric Wilcoxon test.

## Results

### Patient characteristics

A total of 61 patients with newly diagnosed NHL were enrolled prospectively in the study. Patients' characteristics are summarized in Table 1. Median age was 58 years (range 18–90 years) and 59% of patients (n = 36) were male; 42 (68.9%) patients had diffuse large B-cell lymphoma, 6 (9.8%) follicular lymphoma (grade III), 4 (6.6%) mantle-cell lymphoma, 7 (11.5%) marginal-zone lymphoma and 2 (3.3%) T-cell NHL.

Twenty (32.8%) of those had stage IV disease, and 10 (16.4%) stage III, 12 (19.7%) stage II and 19 (31.1%) stage I disease. Twenty-one patients (34.4%) had B-symptoms prior to treatment initiation. Fifty-four patients (88.5%) received R-CHOP (47 every 21 days and 7 every 14 days), 4 (6.6%) received R-CVP and 3 (4.9%) CHOP as first-line therapy for their disease. Twenty-three patients (37.6%) received 6 cycles of first-line therapy and 38 (62.4%) a total of 8 cycles.

### Bone mineral density and bone remodeling markers

At baseline, NHL patients had a median T-score of L1-L4 BMD of  $-0.71$  (range  $-4.27$  to  $+4.36$ ) and of FN BMD of  $-0.79$  ( $-4.01$  to  $+2.49$ ). The median T-score of the lumbar vertebra

Table 1	
Patient's Clinical Characteristics	
Patients Characteristics (N=61)	
Gender (male/female)	36 (59%)/25 (41%)
Age (range/median)	18–90/58
Disease	DLBCL 42 (68.9%) FL GR III 6 (9.8%) MCL 4 (6.6%) MZL 7 (11.5%) T-NHL 2 (3.3%)
Stage	I 19 (31.1%) II 12 (19.7%) III 10 (16.4%) IV 20 (32.7%)
Symptoms	A 40 (65.6%) B 21 (34.4%)
Therapy	R-CHOP-21 47 (77%) R-CHOP-14 7 (11.5%) R-CVP 4 (6.6%) CHOP 3 (4.9%)
Cycles	6 23 (37.6%) 8 38 (62.4%)

DLBCL = diffuse large B cell lymphoma, FL GR III = follicular lymphoma Grade 3, MCL = mantle cell lymphoma, MZL = marginal zone lymphoma, T-NHL = T-cell Non-Hodgkin's Lymphoma.

with the major bone loss (the vertebrae with the lowest T-score) was  $-1.41$  ( $-4.6$  to  $+3.83$ ; Table 2). The administration of chemotherapy resulted in a dramatic reduction (57% change from pre-chemotherapy value) of BMD in L1-L4 (median T-score:  $-1.12$ ; range  $-4.49$  to  $+4.34$ ;  $p=0.001$  and median T-score of the lumbar vertebra with the major loss: median T score  $-1.45$  (2.8% change from pre-chemotherapy value); range:  $-4.84$  to  $+2.9$ ;  $p=0.001$ ) and in a less impressive reduction in FN BMD (20% change from pre-chemotherapy value) (median T-score:  $-0.95$ ; range:  $-3.68$  to  $+2.12$ ;  $p=0.0001$ ) compared to baseline values.

At baseline patients had decreased levels of OC 0.6 ng/ml vs 10.41 ng/ml in controls ( $p=0.001$ ) and increased levels of TRACP-5b (1.82 U/L in patients vs 1.52 U/L in controls,  $p=0.005$ ). There were no differences in the other markers of bone metabolism. There was a strong correlation between L1-L4 and FN BMD ( $r=0.64$ ,  $p<0.0001$ ) as well as between L1-L4 BMD and Dkk-1 ( $r=-0.617$ ,  $p<0.0001$ ) and between CTX with TRACP-5b ( $r=0.65$ ,  $p<0.0001$ ) and sRANKL ( $r=0.413$ ,  $p=0.036$ ). There was no correlation between BMD and NHL stage (Table 3).

The reduction of L1-L4 BMD post-chemotherapy and of vertebrae BMD with major loss was more profound in males ( $p=0.001$ ) than in females ( $p=0.004$ ) and in patients of  $>55$  years

( $p=0.0001$ ) compared to all others ( $p=0.015$ ). Patients who received 8 cycles of chemotherapy had a greater reduction of L1-L4 ( $p=0.0001$ ) and of vertebra with major loss ( $p=0.003$ ) and FN ( $p=0.0001$ ) compared to patients who received 6 cycles of chemotherapy. This reduction was irrespective of the NHL stage (I/II vs III/IV) (Fig. 1).

The administration of chemotherapy also resulted in a dramatic increase of CTX (6.93 ng/ml vs 0.6 ng/ml,  $p=0.008$ ) but no similar increase was seen for the sRANKL/OPG ratio. Both markers of bone formation, bALP (26.24 U/L vs 19.03 U/L,  $p=0.0001$ ) and OC (18.62 ng/ml vs 0.6 ng/ml,  $p=0.0001$ ) were increased. Dkk-1 and TRACP-5b also increased post-therapy (192.23 pmol/L vs 166.56 pmol/L,  $p=0.005$  and 2.78 U/L vs 1.82 U/L,  $p=0.0001$ ), respectively (Fig. 2).

There was a greater increase of CTX ( $p=0.04$ ), sRANKL/OPG ( $p=0.015$ ), TRACP-5b ( $p=0.03$ ), bALP ( $p=0.003$ ) and OC ( $p<0.0001$ ) in patients who received 8 cycles of chemotherapy compared to all others. During study period, one patient had a pathological fracture in his right FN.

## Discussion

Our study suggests that first-line chemotherapy results in high bone turnover, which leads to increased bone loss and reduced BMD of L1-L4 and FN in NHL patients. All studied markers of bone remodeling, with the exception of OPG and sRANKL, were significantly increased in patient post-chemotherapy compared to controls. During study period, one male patient had a pathological fracture in his right FN and overall the decline in BMD was more profound in males compared to females.

Other groups have demonstrated bone loss post-chemotherapy in lymphoma patients.

Paccou et al studied bone loss in 32 adult patients with lymphoma with BMD at baseline better than  $-2.5$  by T or Z scores and demonstrated that they experienced significant bone mineral density loss post-chemotherapy. They also report that female gender, higher lactate dehydrogenase, lower creatinine clearance, lower albumin, higher corrected calcium and lower alkaline phosphatase were independently associated with BMD loss. A Surveillance, Epidemiology, and End Results (SEER)-Medicare Linked database analysis of a 11-year up follow up in 13,570 patients aged  $\geq 65$  also showed that the use of chemotherapy was significantly associated with increased risk of fracture and osteoporosis in elderly patients with non-Hodgkin lymphoma.<sup>16</sup> A recent study retrospectively assessed BMD in long-term lymphoma survivors who had undergone high-dose therapy with autologous transplant and found BMD to be close to normal for their respective age. Findings may point to

Table 2				
BMD and Bone Remodeling Markers				
Area	Pre-chemo	Post-chemo	p	Percentage change in BMD T-score
L1-L4				
BMD T-score (median)	$-0.71$	$-1.12$	0.0001	$-57\%$
BMD T-score (range)	$-4.27$ to $+4.36$	$-4.49$ to $+4.34$		
Lumbar Vertebra with the major bone loss (LV-MBL)				
BMD T-score (median)	$-1.41$	$-1.45$	0.0001	$-2.8\%$
BMD T-score (range)	$-4.6$ to $+3.83$	$-4.84$ to $+2.9$		
FN				
BMD T-score (median)	$-0.79$	$-0.95$	0.0001	$-20\%$
BMD T-score (range)	$-4.01$ to $+2.49$	$-3.68$ to $+2.12$		

BMD = Bone mineral density.

**Table 3****Comparison of Markers of Bone Mineral Density Between Controls and Patients, Pre- and Post-Chemotherapy**

	Min	Max	Mean	Median	p value
CTX (ng/ml)					
Controls	ND	2.92	0.68	0.52	0.341
Pre-chemo	0.04	2.3	0.71	0.6	
Post-chemo	0.14	2.61	0.95	6.92	0.008
Osteocalcin (ng/ml)					
Controls	2.9	61.34	13.67	10.41	0.001
Pre-chemo	0.66	47.55	0.71	0.6	
Post-chemo	1.29	60.86	20.94	18.62	0.0001
OPG (pmol/L)					
Controls	1.75	16.37	4.59	3.78	0.686
Pre-chemo	ND	25.25	5.78	3.74	
Post-chemo	0.26	24.61	5.73	4.34	0.913
BALP (U/L)					
Controls	12.24	39.54	21.37	19.23	0.752
Pre-chemo	9.78	39.43	21.62	19.03	
Post-chemo	14.08	57.8	27.8	26.24	0.0001
RANKL (pmol/L)					
Controls	ND	7.0	0.58	0.43	0.866
Pre-chemo	ND	2.78	0.46	0.42	
Post-chemo	ND	4.44	0.68	0.38	0.349
TRACP-5b (U/L)					
Controls	0.09	2.93	1.39	1.52	0.005
Pre-chemo	0.16	4.33	1.92	1.82	
Post-chemo	0.06	7.84	2.9	2.78	0.0001
DKK1 (pmol/L)					
Controls	55.22	258.76	149.2	147.4	0.142
Pre-chemo	40.05	1252.18	193.23	166.56	
Post-chemo	82.81	1721.74	244.18	192.23	0.005
RANK/OPG					
Controls	0.0	0.53	0.11	0.09	0.875
Pre-chemo	0.0	1.7	0.18	0.08	
Post-chemo	0.0	0.67	0.14	0.09	0.739

The p value in the control line refers to differences between controls and subjects pre-treatment, while p value in the post-chemo line refers to differences among patients before and after treatment.

bALP = bone specific alkaline phosphatase, CTX = carboxy-terminal cross-linking telopeptide of type I collagen, Dkk-1 = osteoblast inhibitor dickkopf-1, ND = non detectable, OC = osteocalcin, sRANKL/OPG ratio = soluble receptor activator of nuclear factor B ligand/osteoprotegerin, TRACP-5b = 5b isoenzyme of tartrate-resistant acid phosphatase.

a recovery of normal bone metabolism in the long term in these patients.<sup>17</sup> Pretreatment vertebral bone density was found to decrease post-treatment with R-CHOP (like) regimens in 111 lymphoma patients and to be independent of age.<sup>18</sup> In addition, BMD remained significantly lower even 2 years post-treatment and 14% developed vertebral compression fractures (only L3 was evaluated).

The relationship between glucocorticoids and bone loss is well established and is more pronounced in the spine and trabecular bone than in the femur and cortical bone.<sup>10,19</sup> Standard R-CHOP protocols include 500 mg of prednisone per cycle. As discussed by Ruchlemer et al the standard R-CHOP steroid dose exceeds  $\geq 7.5$  mg/day for more than 3 months which is the threshold of prednisone dose recommended by the American College of Rheumatology for prophylactic bisphosphonate use.<sup>20,21</sup>

The therapeutic efficacy of bisphosphonates via inhibition of osteoclastic bone resorption and their therapeutic efficacy in many malignancy related bone conditions is well established.<sup>22,23</sup> The efficacy of prophylactic bisphosphonate use in NHL patients has been demonstrated in 2 studies, but standard recommendations and guidelines remain absent.

In the phase III RCT by Thompson et al in untreated NHL patients, among individuals screened for baseline BMD, 10% had osteoporosis and 54% had osteopenia or osteoporosis. Seventy-four patients were randomized to receive oral calcium and

vitamin D vs oral calcium, vitamin D and zoledronic acid and biomarkers were collected at baseline, 3, 6, 9, and 12 months after enrolment.<sup>24</sup> BMD remained stable for the group that received ZA compared to the control group which demonstrated BMD deterioration. In addition, N-telopeptide (CTX) and serum b-ALP (BAP) were higher in the control arm at all intervals after treatment. Based on these results the group recommends BMD screening at baseline and calcium, vitamin D and ZA or potentially other bone directed therapies. Kim et al administered pamidronate every 3 months and reported a reduction in bone risk and risk of new vertebral fractures in lymphoma patients receiving chemotherapy.<sup>25</sup> A recent pilot study was designed to assess bone loss in 181 adult patients with hematological malignancies with DXA (dual-energy X-ray absorptiometry) and reports that 67% of patients with Non-Hodgkin lymphoma showed bone loss. Measurements were performed in patients who were pre-treated and had received chemotherapy and in patients prior to treatment initiation. Major differences in BMD were found, as measured by Z-scores, compared to normal age-matched population for L1 but not for L2-L4, which were more prominent for the NHL patients. They attribute this difference to the negative effect of cancer therapies, which includes steroids, on BMD in NHL patients as compared to patients with CLL/SLL.<sup>20</sup>

Other options that could be considered are the monoclonal antibody against the RANK-ligand denosumab or other agents

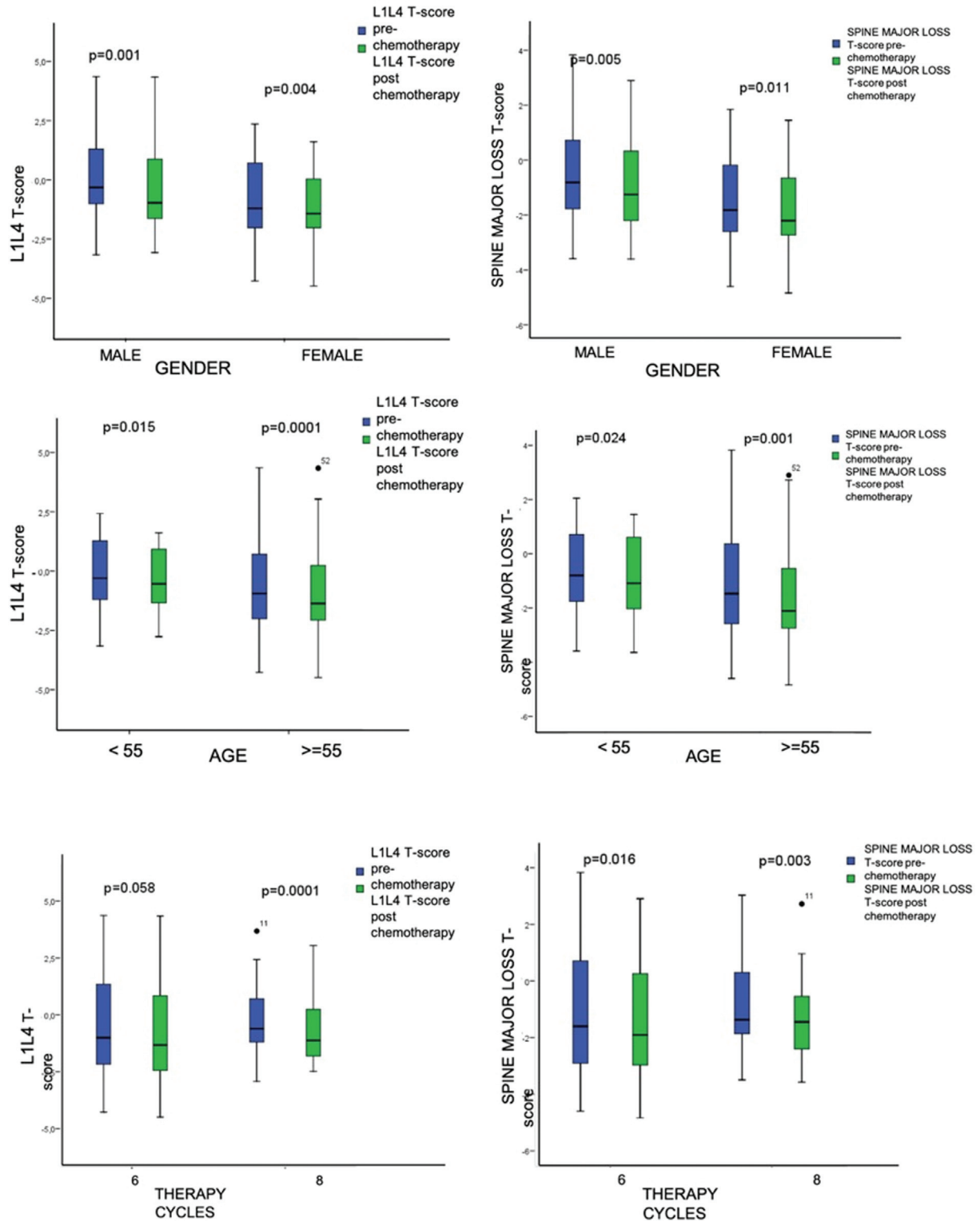
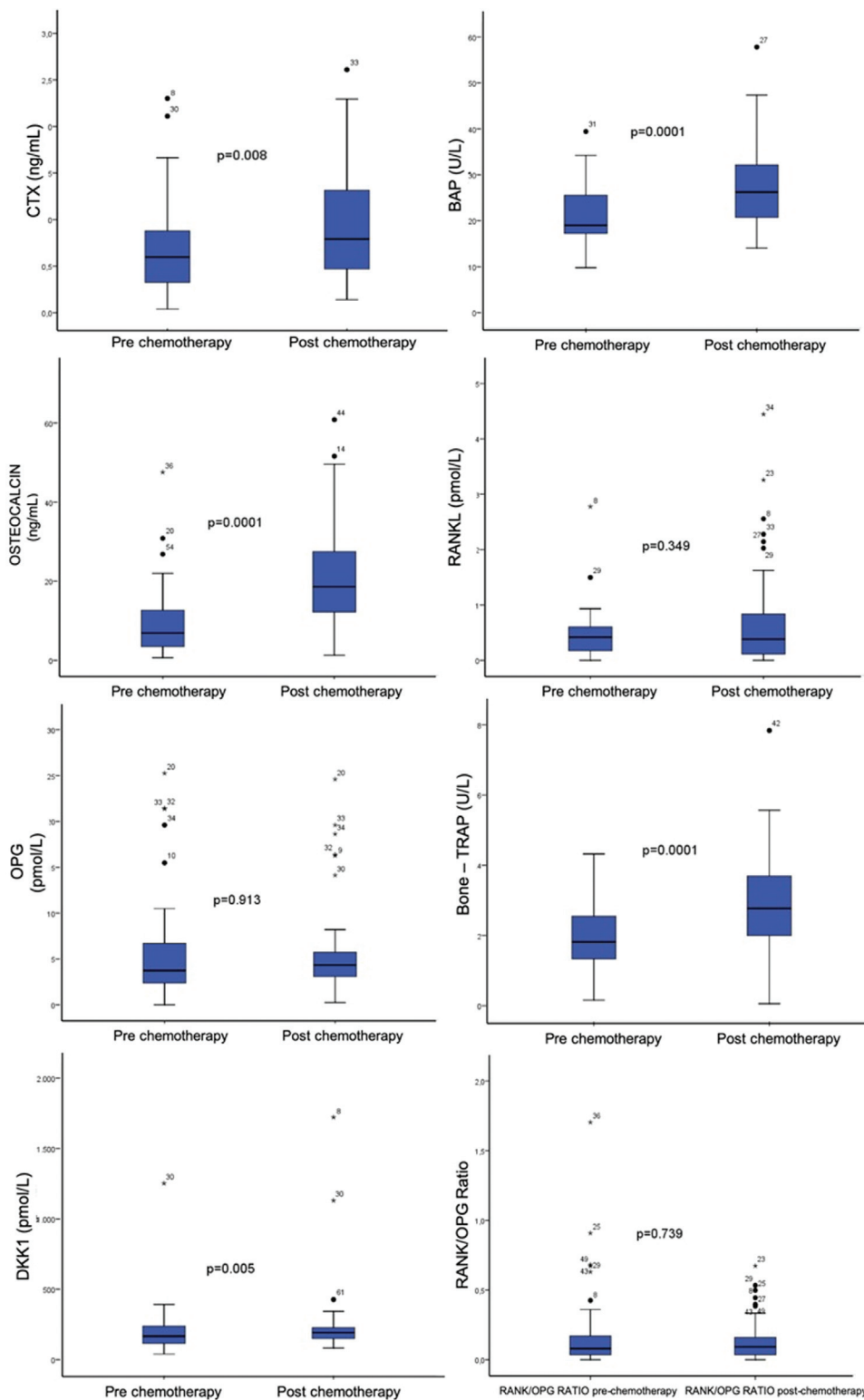


Figure 1. Box plots comparing L1-L4 BMD and vertebrae BMD based on sex, age, and number of treatment cycles. BMD= Bone mineral density.

with anti-Dkk-1 activity together with calcium and vitamin D may be useful for preventing bone loss in these patients.<sup>26-28</sup> Screening of bone mineral density (BMD) is not currently included in NCCN lymphoma patient management guidelines but is recommended for patients receiving long term corticosteroids and chemotherapy by several groups.<sup>29</sup>

The administration of chemotherapy also resulted in a dramatic increase of CTX (6.93 vs 0.6,  $p=0.008$ ). CTX is a marker of osteoclast activity and therefore, its increase points to increased bone resorption post-chemotherapy. It indicates metabolic activity and it increased in diseases such as rheumatoid arthritis and osteoarthritis.<sup>30,31</sup> sRANKL directly induces osteoclast



**Figure 2. Box plots showing the changes in markers of bone mineral density pre and post-chemotherapy.** bALP = bone specific alkaline phosphatase, CTX = carboxy-terminal cross-linking telopeptide of type I collagen, Dkk-1 = osteoblast inhibitor dickkopf-1, OC = osteocalcin, sRANKL/OPG ratio = soluble receptor activator of nuclear factor B ligand/osteoprotegerin, TRAP = 5b isoenzyme of tartrate-resistant acid phosphatase.

differentiation and proliferation and OPG is a soluble decoy receptor for RANKL and one of the most potent antiresorptive agents. Their ratio (sRANKL/OPG) plays a major role in osteoclastogenesis and it has been shown to increase in patients

with bone and multiple myeloma<sup>15</sup> but it does not become abnormal in these patients following chemotherapy. BMD decline is therefore not associated with altered production of RANKL or OPG. Dkk-1 is a soluble inhibitor of the Wnt/beta-catenin

signaling which is central to bone development and hemostasis. Overexpression of Dkk1 in osteoblasts causes osteopenia and Dkk1 inhibits fracture repair and studies have shown that Dkk-1 activation is the underlying cause of glucocorticoid and estrogen deficiency mediated osteoporosis.<sup>32</sup> Post-treatment an increase in Dkk-1 levels was also seen in our cohort (192.23 pmol/L vs 166.56 pmol/L,  $p=0.005$ ). TRACP-5b is secreted by osteoclasts and is elevated in patients with osteoporosis, with bone loss and in patients with bone metastasis. TRACP-5b was increased post-therapy in our cohort (2.78 U/l vs 1.82 U/l,  $p=0.0001$ ).<sup>33,34</sup> Markers of bone formation, bALP and OC also increased post-chemotherapy, indicating increased bone turnover. Chemotherapy therefore affects bone metabolism and as a result stimulates bone remodeling. To our knowledge no other group has measured markers of bone metabolism in such cohort pre- and post-chemotherapy in a systematic manner.

It should be noted that our analysis included patients with T-scores  $<-2.0$  across all measured sites at baseline. A proportion of the population had therefore a diagnosis of osteoporosis or osteopenia prior to treatment initiation. The effect of chemotherapy on BMD decline is potentially affected by the inclusion of these patients but is a true effect as it is observed across all ranges of BMD in our cohort. A larger number of patients could allow subgroup analysis based on baseline BMD to delineate the effect of chemotherapy based on initial bone health.

We have also to mention that we assessed biomarkers of bone metabolism and changes in BMD approximately 6 months post-chemotherapy initiation. Following up with re-evaluation at 12 months would have provided a more complete picture of the short- and long-term effects of chemotherapy on bone health and the potential reversal of these effects. The larger decline in BMD post-chemotherapy in male vs female patients cannot be fully explained but could be potentially linked to the suppression of the androgen axis by chemotherapy. Patients with CrCl  $< 60$  ml/min were excluded from the study to avoid the confounding effect of impaired renal function on bone metabolism. It should be however noted that excluding this subpopulation makes our cohort less representative of the real world population.

The negative impact of chemotherapy on BMD has been demonstrated previously by other groups in small cohorts of patients. A detailed study of the effect of chemotherapy on markers of bone remodeling in patients with NHL has not however been previously reported. The results of our study further emphasize the need to address the issue of bone health in NHL patients in a more systematic manner. Our data needs to be verified in larger cohorts that will allow subgroup analysis to determine the assessment modality and the most appropriate location of the lumbar spine to be assessed. More systematic data collection and analysis is required to establish what dosing regimens of glucocorticoids and chemotherapeutic regimens are most associated with bone loss and would allow careful selection of patients who would benefit from prophylactic anti-resorptive agent use.

Future verification of the effects of chemotherapy on markers of bone metabolism could shed light on the underlying mechanisms and allow the identification of an appropriate marker to assess the effect of chemotherapy on bone health. RCTs to assess the prophylactic use of bisphosphonates and newer agents in this setting would then allow incorporation of BMD screening and administration of prophylaxis in the management of NHL and other lymphoma patients.

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