BONE MINERAL DENSITY AFTER TREATMENT OF NON-HODGKIN'S LYMPHOMA IN CHILDHOOD

Aysu Duyan ÇAMURDAN[1], Aynur OĞUZ[2], Alev HASANOĞLU[3], Ceyda KARADENİZ[2], M.Orhun ÇAMURDAN[1], Nurten TÜRKÖZKAN[4], Mustafa ÜNLÜ[5]

Purpose: To investigate the side effects of cytotoxic drugs on bone mineral density in children with non-Hodgkin's lymphoma.

Materials and Methods: A cross-sectional study was conducted. The patient group was composed of 31 (6 girls and 25 boys) non-Hodgkin's lymphoma patients who had completed their therapy. The control group was composed of 30 (11 girls and 19 boys) healthy children. The bone mineral density of the vertebrae (BMD-V) and femur (BMD-F) and biochemical parameters of bone turnover were studied in both groups.

Results: The patient and control groups were statistically similar in terms of age, sex, body weight, height, pubertal status, and laboratory parameters (p >0.05). Mean bone mineral density values (g/m2) in the patient group were lower than those in the control group, but not significantly so (respectively, BMD-V: 0.574±0.188 g/cm2, BMD-F: 0.658±0.191 g/cm2 vs. BMD-V: 0.644±0.158 g/cm2, BMD-F: 0.718±0.128 g/cm2, p>0.05).

Conclusion: Although there was no significant difference between bone mineral density measurements of the patients and controls, the lower levels of bone density in patients could indicate that the bone mineral density of patients with non-Hodgkin lymphoma was affected by cytotoxic therapy. This should be taken into consideration in the follow-up of such children.

Key Words: Non-Hodgkin's lymphoma, bone mineral density, chemotherapy, children.

ÇOCUKLUK ÇAĞI NON- HODGKIN LENFOMA TEDAVİSİ SONRASI KEMİK MİNERAL DANSİTESİ

Amaç: Bu çalışma non-Hodgkin lenfomalı çocuklarda kullanılan sitotoksik ilaçların kemik mineral dansitesi üzerindeki yan etkilerini araştırmak amacıyla planlandı.

Gereç ve Yöntemler: Kesitsel bir çalışma yürütüldü. Hasta grubu 31 (6'sı kız, 25'i erkek) tedavisi tamamlanmış non-Hodgkin lenfomalı olgudan oluşuyordu. Kontrol grubu 30 (11'i kız, 19'u erkek) sağlıklı çocuktan oluşturuldu. Her iki grupta da vertebra ve femur kemik mineral dansite ölçümleri kemik döngüsünü gösteren biyokimyasal parametreleri incelendi.

Bulgular: Hasta ve kontrol grubundaki olguların yaşları, cinsiyetleri, vücut ağırlıkları, boyları, puberte evreleri, laboratuvar parametreleri istatistiksel olarak benzerdi. Hasta grubunun ortalama kemik mineral dansitesi (g/m2) kontrol grubundan düşük olmasına karşın fark istatistiksel olarak anlamlı değildi (sırasıyla, BMD-V: 0,574±0,188 gr/cm2, BMD-F: 0,658±0,191 gr/cm2 vs BMD-V: 0,644±0,158 gr/cm2, BMD-F: 0,718±0,128 gr/cm2 , p>0.05).

Sonuç: Bu çalışmada hasta ve kontrol grupları arasında istatistiksel anlamlı fark bulunmamasına karşın hasta grubundaki düşük kemik minarel dansitesi ölçümü non-Hodgkin lenfoma'lı çocukların kemik yoğunluğunun sitotoksik tedaviden etkilenebileceğini düşündürmektedir.

Anahtar Kelimeler: Non-Hodgkin lenfoma, kemik mineral dansitesi, kemoterapi, çocuk.

[1] Gazi University, Medical School, Clinic of Pediatrics, [2] Professor. Gazi University, Medical School, Department of Pediatric Oncology, [3] Professor. Gazi University, Medical School, Department of Pediatric Metabolism, [4] Professor. Gazi University, Medical School, Department of Medical Biochemistry, [5] Professor. Gazi University, Medical School, Department of Nuclear Medicine Ankara, Turkey

INTRODUCTION

With the improvements over the past 30 years, children who receive anti-cancer chemotherapy survive into adulthood (1, 2). It has been postulated that 1/250 of adults over 25 years of age will be treated for a childhood cancer by the year 2010 (3). As the survival rates increase, the long-term side effects of cytotoxic therapy like endocrine system dysfunction, cataracts, renal dysfunction, secondary malignancies, psychological problems and osteoporosis are becoming more important (1, 2, 4-8).

Osteoporosis is defined as a decrease in bone mineralization and causes morbidity, mortality and financial problems (9-11). Because childhood bone mass is the main determinant of an adulthood bone fracture (7, 12, 13) and new advances in osteoporosis focus on its prevention more than its therapy (10, 14-18), osteoporosis should be taken into serious consideration in patients with childhood cancer.

With the advances in supportive care and new regimens, the success rate in non-Hodgkin's lymphoma (NHL) treatment has reached 80% and thus the importance of osteoporosis has doubled because of this high survival rate (1, 2, 4-8, 19).

PATIENTS AND METHODS

This study was performed in Gazi University Medical School Department of Pediatric Oncology between 1995 and 1997. The study included 31 NHL patients (6 girls and 25 boys) aged 4.5-18.0 (9.0 ± 3.8) years whose body weight and height were in normal ranges, and 30 healthy children (11 girls and 19 boys) aged 4-15 (9.4±3.2) years whose age, sex, height, weight and pubertal status were well matched with those of the patients. Pubertal status determination was based on the Tanner scale (20, 21). The local ethics committee approved the study.

Among the patients, 26 had small non-cleaved cell lymphoma (21 Burkitt and five non-Burkitt), three had large cell lymphoma, and two had lymphoblastic lymphoma, with three of them at stage II, 19 at stage III, and six at stage IV. The primary involvement area was the abdomen in 23 patients (74.1%), the head and neck in 12 patients (38.7%), and the mediastinum in 10 patients (19.3%). Twenty-seven of them were treated according to BFM-90, two according to LSA2L2 and two according to LMT-89 protocols; none of them had received radiotherapy. The duration of therapy was 3-12 months (6.0 ± 3.4). Three patients (9.7%) had fractures in the lower extremity and four (12.9%) had bone pain during or after therapy.
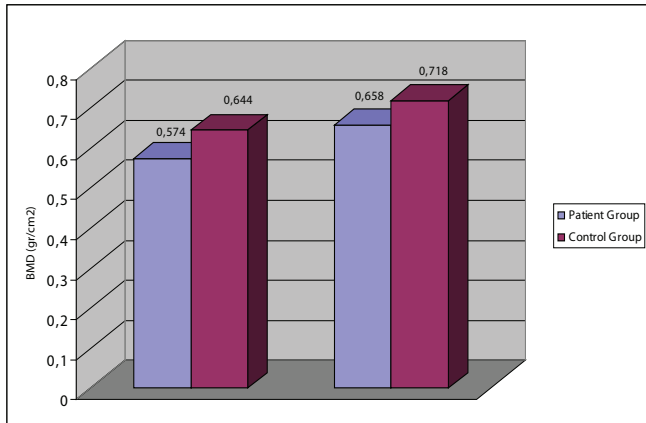
Figure 1: Mean BMD values in the patient and control groups.

The cumulative doses of dexamethasone, ifosfamide, prednisolone (systemic and intrathecal) and methotrexate (MTX) (systemic and intrathecal) given to the patients are shown in Table 1.

Fasting blood samples were obtained from all subjects in the morning while none of them had received steroids or antibiotics for the previous 48 hours. Serum total calcium (tCa), inorganic phosphorus (P), magnesium (Mg), creatinine (Cr) and alkaline phosphatase (ALP) levels were measured with a Technicon RA-XT (Swords Co, IRELAND) analyzer using ortocrezolphytalein complexone, phosphomolibdat, calmogite Mg Complex, paranitrophenile phosphate and Jaffe methods respectively (22), while intact parathormone (PTH), osteocalcine and calcitonine levels were measured using a DSL-8000 ACTIVETM Intact PTH IRMA kit (Diagnostic Systems Laboratories, Inc, Texas, USA), DSL-6900 Osteocalcine Radio immunoassay kit (Diagnostic Systems Laboratories, Inc, Texas, USA) and DSL-5200 Ultra-sensitive Calcitonine Radio immunoassay kit (Diagnostic Systems Laboratories, Inc, Texas, USA). Cr, Mg, P and tCa were also measured and glomerular filtration rate (GFR), tubular phosphate reabsorption (TPR), and Ca excretion were calculated from the 24-hour urine samples (23). Bone mineral density (BMD) was measured from the 2nd to the 4th lumbar vertebrae (BMD-V) and

Table 1: The cumulative doses of the chemotherapoetic agents used in patients.*

MTX® (n=31)	Prednisolone (n=31)	Dexamethasone (n=26)	Ifosfamide (n=26)	IT$^\perp$ Prednisolone (n=31)	IT$^\perp$ MTX (n=31)
1.0-30.0 (9.8±7.5)	0.15-2.90 (0.42±0.21)	0.30-12.00 (0.45±0.18)	8.0-24.0 (11.4±3.3)	0.07-0.42 (0.20±0.08)	0.04-0.22 (0.10±0.04)

*: All values are given as g/m², $\perp$: Intrathecal, ®: Methotrexate

Table 2: Anthropometric and laboratory parameters of the patient and control groups.

Anthropometric parameters		Patient Group (n:31)	Control Group (n:30)	p
Age (year) mean±SD		9.0 ± 3.8	9.4±3.2	0.38
Gender (Female/Male)		6/25	11/19	0.46
Height (cm) mean±SD		129.2±21.3	136.3±18.3	0.12
Weight (kg) mean±SD		30.8±14.3	34.8±13.8	0.34
Laboratory parameters and normal ranges for age parameters				
Ca (mg/dl)	8.2-10.6	10.1±1.7	10.0±0.8	0.56
P (mg/dl)	2.5-4.5	5.4±1.9	4.5±0.7	0.34
ALP (U/l)	145-420	220.1±81.9	192.0±54.3	0.14
Mg (mg/dl)	1.5-2.3	1.9±0.4	2.0±0.6	0.54
Osteocalcine (ng/ml)	5-60	17.7±12.9	12.9±10.8	0.18
Calcitonine (pg/ml)	<25-70	20.7±16.0	17.8±10.1	0.16
PTH(intact) (pg/ml)	10-55	33.1±17.5	29.9±14.3	0.24
GFR (ml/m/1.73m²)*	89-165	114.7±37.8	105.3±20.2	0.16
*TPR**(%)*	83-98	86.6±7.6	88.8±6.0	0.50
Calciuria (mg/kg/d)	>4	2.2±1.6	2.9±1.4	0.46

*GFR: Glomerular Filtration Rate, **TPR: Tubular phosphate reabsorption, p >0.05

femur neck (BMD-F) using dual energy X- ray absorptiometry (DEXA) (NORLAND XR -35) (25).

Statistical analyses were performed using SPSS for Windows with the chi-square, Student-t test and Pearson correlation analyzing systems.

RESULTS

The patient group was similar to the control group in terms of age, sex, body weight, height and pubertal status (p > 0.05).

The serum Ca, P, Mg, ALP, osteocalcine and calcitonine levels of all patients were at normal levels. All patients but one had normal tubular phosphate reabsorption rates and three had hypercalciuria and elevated intact PTH values. The patient and control groups were statistically similar with regard to their blood and urine measurements (p >0.05). The age, sex, body weight, height, and laboratory parameters of both groups are given in Table 2.

BMD measurements of the groups are given in Figure 3. The BMD values of the patient group were lower than those of the control group although not significantly so (respectively, BMD-V: 0.574±0.188 g/cm2, BMD-F: 0.658±0.191 g/cm2 vs. BMD-V: 0.644±0.158 g/cm2, BMD-F: 0.718±0.128 g/cm2, p>0.05).

There was no correlation between the BMD values and the type, duration, dose of chemotherapy and time interval after the end of therapy (p>0.05).

DISCUSSION

Although there are numerous studies on childhood leukemia concerning the abnormalities in BMD as a result of primary illness, cranial radiotherapy and cytotoxic chemotherapy (5, 12, 13, 25-36), there are relatively few investigations on childhood NHL (1, 7, 34).

Clinical manifestations of BMD abnormalities seen in patients with malignancy are bone pain, fracture and movement disorders (8, 37-39). The patients in this study showed similar manifestations: 6.7% of them had bone ache and 12.9% of them had pathologic fractures. Atkinson et al (32), in their study in patients with leukemia, found that 70% of them had low BMD values, which was attributed to the side effects of chemotherapy on bone mineral metabolism because all of the patients were in remission. They also found that fracture incidence was 64% for the first 6 months after therapy, and then it decreased to 39% for the same patients. These data show that side effects of therapy on bone metabolism are time dependent. O'Regan et al (38) and Ragab et al (39) support this postulation with their studies on patients with leukemia.

In the present study, although the difference was not significant, patients who completed the chemotherapy protocols had a tendency to have lower mean BMD values compared to the controls.

Hahn et al (40, 41) and Zonneveld et al (42) showed that patients treated with corticosteroid or MTX for non-neoplastic diseases had lower BMD values, supporting the idea that problems in bone metabolism seen in patients with malignancy originate from the therapies used, not from the primary illnesses.

The effect of chemotherapeutic agents' side effects on bone metabolism influence both trabecular and cortical bone tissue (30, 36, 43, 44). In our study, the patient group had similar percentages for BMD-V (representing trabecular bone) and BMD-F (representing cortical bone), confirming that cortical and trabecular bones are equally affected.

In this study, no correlations were found between BMD values and the duration or dose of the chemotherapeutic agent. In the literature, there are conflicting results; some authors postulate that the decrease in BMD is dose and/or time dependent (13, 40, 44), but others do not support this statement (35, 43).

The underlying mechanism of the side effects of chemotherapeutics on bone mineralization remains unclear and is supposed to be multifactorial (6-8). MTX, corticosteroids and ifosfamide inhibit active vitamin D production, leading to Ca malabsorption and thus contributing to a decrease in serum Ca. This in turn causes an increase in serum PTH, leading to increased bone resorption (8, 41). In this study, only three patients in the patient group had slightly high PTH levels. Similarly, Atkinson et al (37) found PTH values to be normal in all of their leukemia patients and postulated that decreased BMD values in their patients were due to MTX and steroid-induced renal loss and intestinal malabsorption of Mg from the intestine, leading to hypomagnesemia and related hypocalcemia triggered by MTX and steroids. In our study, serum Mg levels were normal in a vast majority of patients. Rickers et al (44) and Schepper et al (45) also found normal Mg and Ca levels in their patients with decreased BMD values. Another antineoplastic agent known to have deleterious effects on bone metabolism is ifosfamide. Its toxicity originates from the effects on renal proximal tubules, leading to hyperphosphaturic hypophosphatemia, hypercalciuria and hyperparathyroidism (2, 7, 44). In our study, all patients but one had normal TPR rates and three had hypercalciuria and elevated PTH values. These data show that the underlying mechanism cannot be explained by only one manifestation, but by the combination of all and other unknown factors.

At this point, the time elapsing for the compensatory mechanisms to take place becomes a matter of importance. The studies in the literature do not give an exact time interval between the end of chemotherapy and the prevalence of deleterious effects of them on BMD, and thus the measurable parameters of compensatory mechanisms. Studies designed several years after the end of chemotherapy find no difference in BMD values (1). This supports the hypothesis that changes in BMD occur slowly and need more than several years to take place. In our study, the time interval based on a wide range (1-52 months) also makes interpretation difficult. The finding

that biochemical parameters do not match the logical expectations and that BMD changes are not statistically significant may be the result of this wide range of time interval. For some patients, the time that elapsed after the chemotherapy may not have been sufficient for the effects of therapeutic agents to take place. On the other hand, for some other patients, it could have been long enough for the compensatory mechanisms to take place and return the values to normal ranges. In order to clarify this matter, studies having homogeneous time intervals between the end of the therapy and the time of the measurements are needed.

In conclusion, the findings of our study indicate that BMD may have been affected by the cytotoxic therapy used for the treatment of children with NHL, and this point should be taken into consideration during the follow-up of such children. Studies with more patients, together with a homogeneous time interval between the end of therapy and the time of the measurements, are needed to test this hypothesis.

Correspondence Address
Aysu Duyan Çamurdan
Address: Devlet Mah. Devrimler Cad. 359. sokak Yeşilöz sitesi 2/5
Eryaman. Ankara-Turkey
Tel: 312-214 10 90 / 6019   Fax: 312-213 36 43
E-Mail: aysucamurdan@yahoo.com

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