Bone Mineral Density in Children with Relapsing Nephrotic Syndrome

M. Basiratnia, M.H. Fallahzadeh, A. Derakhshan, G. Hosseini-Al-Hashemi

Abstract

Background: Given the high relapse rate of disease in children with steroid dependent nephrotic syndrome and the osteoporotic effect of long periods of steroid therapy, this survey was performed to find the bone mineral status of these patients.

Methods: Bone mineral density and content (BMD and BMC) were measured using Dual energy X-ray absorptiometry in 37 nephrotic children, six girls and 31 boys aged from four to 21 yrs, as patient group and 37 age and sex-matched healthy individuals as control group. Historical data were collected by chart review.

Results: As compared to the control group, the patients were shorter in stature. The percentage of BMC of lumbar and BMD of femoral bones of the patients was significantly lower than control group. According to the Warner method, 12% of the patients were osteoporotic and the BMD of their femoral and lumbar bones was inversely correlated with cumulative steroid dose.

Conclusion: Bone loss can occur in some steroid-dependent nephrotic patients, especially those with low age of onset and those with longer duration of the disease and higher cumulative dose of steroid. Therefore, measurements of BMD and BMC could be recommended, at least, for the selected patients.

Keywords ● BMD ● nephrotic syndrome ● osteoporosis ● corticosteroid

Introduction

Steroid-dependent nephrotic syndrome (SDNS) is one of the most common causes of childhood referral to pediatric nephrologists, which due to its relapsing course, long term steroid treatment is inevitable. Corticosteroids directly and indirectly contribute to derangements in calcium and bone metabolism with frequent loss of vitamin D metabolites in the urine.

Although bone demineralization is a well-known side effect of long term corticosteroid therapy, previous studies showed conflicting results in relation to SDNS. It is not clear how and in which group of patients preventive measures should be taken to protect bone mineralization. Therefore, this study was designed to determine the bone mineral status of the nephrotic patients compared to age and sex-matched healthy individuals.
as control group as well as to what is considered normal for their body size and pubertal stage, to provide preventive and therapeutic measures for patients with SDNS.

Patients and Methods

The present study comprised patients who were followed in pediatric nephrology clinic as steroid-dependent or frequently relapsing nephrotic syndrome. Steroid-dependent nephrotic syndrome was defined as two consecutive relapses during corticosteroid treatment or within 14 days of its cessation. Those who had two or more relapses within six months of initial response or four or more relapses within any 12 months period, were considered as frequent relapers.

Bone mineral density and content (BMD and BMC) of lumbar L1-L4 and femoral neck were assessed in 37 patients with SDNS and in 37 age and sex-matched healthy students selected from Shiraz primary and secondary schools after describing the study and taking a written consent from them or their parents. BMD and BMC were measured by Dual Energy X-ray absorptiometry (DEXA, Lunar DPX, General Electric; USA).

All patients had normal glomerular filtration rate (Schwartz formula) and were treated with prednisolone (60mg/m²/day) for four weeks at the onset, followed by a single dose of 40 mg/m² on alternate days for tapering off during six weeks. The relapses were treated with prednisolone (60 mg/m²/day) until the urine was protein-free for three days, when it was continued with 40 mg/m² every other day for six to eight weeks. However, some patients with relapse were maintained on low daily dose of prednisolone for variable time periods. Other drugs, like levamisole, cyclophosphamide and cyclosporine were used for 18, 8 and 7 patients, respectively. None of the patients received calcium or vitamin D. In a 21-yr-old patient, interpretation of data was based on WHO criteria. As four patients were not cooperative in positioning their legs during the procedure for femoral neck, the assessment of BMD was thus made on 33 patients for the femoral region and 37 patients for the lumbar area. The Warner method was used to compare the lumbar BMC of 32 patients with that of the control group aging from six to 18 yrs.

Statistical analysis

Data are presented as Mean±SD. Statistical analysis was performed using paired Students t-test for comparison of quantitative variables and Pearson correlation for determining the relationship between the variables and P<0.05 was considered significant.

Results

The patients under study comprised six girls and 31 boys, with the means of age and ages at the onset of nephrotic syndrome being 11.9±3.9 yrs and 6.4±3.6 yrs respectively. Other characteristics of the patients are shown in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean±SD</th>
<th>Range</th>
</tr>
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<tbody>
<tr>
<td># of relapses</td>
<td>6.7±5.7</td>
<td>2-21</td>
</tr>
<tr>
<td>Total dose (mg)</td>
<td>1397±11858</td>
<td>1987-57930</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>11.9±3.9</td>
<td>4-21</td>
</tr>
<tr>
<td>Age at onset (yr)</td>
<td>6.4±3.6</td>
<td>2-14</td>
</tr>
<tr>
<td>Duration (yr)</td>
<td>5.3±4.2</td>
<td>0.7-18</td>
</tr>
</tbody>
</table>

As shown in Table 2, the patients were significantly shorter in stature than the control individuals. According to Table 2, the BMD of L1-L4 was the same in both groups; whereas their BMC and %BMC of L1-L4 were significantly different. A significant difference was found between patients and control group in regard to the BMD of femoral neck. Considering WHO criteria, a femoral and lumbar area T scores of less than 2.5 standard deviation, favoring osteoporosis, was found in one patient who was over 18-yrs-old.

<table>
<thead>
<tr>
<th>Characteristics (n)</th>
<th>Patients</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm) (37)</td>
<td>142.1±15.5</td>
<td>149.5±19.2*</td>
</tr>
<tr>
<td>Weight (kg) (37)</td>
<td>38.4±13.3</td>
<td>41.4±15.6</td>
</tr>
<tr>
<td>BMI (kg/m²) (37)</td>
<td>17.7±12.8</td>
<td>18.9±13.8</td>
</tr>
<tr>
<td>Femur BMD (g/cm²) (32)</td>
<td>0.8±0.1</td>
<td>0.9±0.2*</td>
</tr>
<tr>
<td>L1-L4 BMC (g/cm³) (36)</td>
<td>0.7±0.1</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>L1-L4 BMC (%) (32)</td>
<td>104±16</td>
<td>111.5±14.6*</td>
</tr>
<tr>
<td>L1-L4 BMC (g) (32)</td>
<td>25.5±10.5</td>
<td>31.0±16.3*</td>
</tr>
</tbody>
</table>

BMD of the femoral and lumbar area were significantly lower in patients with higher cumulative steroid doses (Fig 1 and 2). In contrary to the duration of disease and the age at onset, we found no correlation between the number of relapses and the prediction of osteoporosis. No correlation was found between cyclosporine treatment and BMD of the femoral and lumbar area in either the patients or the control group. Although, 12% of the patients were osteoporotic, no difference was found between BMD of femoral and lumbar bones in relation to the schedule of steroid therapy (daily or alternate days).
Discussion

The present study showed that osteoporosis found in 12% of the patients was correlated with lower age of disease onset, longer duration of the disease and higher cumulative steroid dose. The adverse effects of corticosteroid on bone mineralization are well established, and are the subjects of several studies with variable results.

In our study decreased BMD of the femoral area and BMC of lumbar bones were apparently in contrast to what was found by Esbjorner et al.\textsuperscript{9} In their cross-sectional study, analysis of nine children treated with a high total steroid dose showed no difference in BMC between the patients and the control group. This discrepancy might be due to the fact that all but one of the patients in the Esbjorner study were in remission phase and were not taking corticosteroid during their investigation.\textsuperscript{9} However, only nine patients were free from steroids in the course of our study. Although, Kano and coworkers showed normal BMD at 16 weeks after steroid withdrawal in the first episode of nephrotic syndrome.\textsuperscript{16} However, there are no substantiated data in regards to normalization of BMD and BMC in patients receiving different and multiple steroid doses. Even though, in Esbjorner et al. study no difference was found between BMD of the patients and control groups, reduced bone turnover and lower growth rate were observed in patients compared to the controls.\textsuperscript{9}

Our results also contrasted with those of Morin and his colleagues who observed no changes in BMD in 29 children treated with corticosteroid.\textsuperscript{17} Also BMC was not reduced in 24 patients with steroid sensitive nephrotic syndrome treated for one, three and six years with corticosteroid.\textsuperscript{5} In the latter study, the patients received calcium and vitamin D, which might have counteracted the demineralization effect of steroid.\textsuperscript{6} Recently, Leonard and coworkers reported that glucocorticoid therapy was not associated with bone loss at the lumbar area after correction for body mass index.\textsuperscript{18} However, they were in agreement with the effect of steroid on bone mineral and quality not captured by bone mineral content.\textsuperscript{18} The results of other investigations supported our findings of bone loss in nephrotic patients.\textsuperscript{8,19,20}

The assessment of BMD in children with acquired glomerular disease treated with corticosteroid showed a significant bone loss even with an alternative dosage schedule.\textsuperscript{20} In these patients, bone density was influenced by the steroid treatment and not by the glomerular diseases.\textsuperscript{20} Lettgen and his colleagues assessed 26 patients with SDNS by quantitative computed tomography and found that bone loss was positively correlated with steroid dosage.\textsuperscript{8} Reugseggar found bone losses in asthmatic patients even with alternate days of steroid therapy.\textsuperscript{19}

Osteoporosis is one the important side effects of steroid treatment and the incidence of steroid-induced osteoporosis was reported to be 30-50% in patients with long-term therapy.\textsuperscript{21} We found that higher cumulative steroid dose is associated with lower BMD and the cause is multifactorial. Corticosteroids directly inhibit osteoblasts and consequently the synthesis of osteoid.\textsuperscript{22} They also decrease intestinal and
BMI in children with relapsing nephrotic syndrome

renal calcium absorption with the resultant secondary hyperparathyroidism leading to increased bone resorption.\textsuperscript{21}

Our observation indicated that the lower age at the onset and the longer duration of the disease were well correlated with greater bone demineralization. This correlation was more pronounced with the lumbar area than with the femoral bone. Lower age and longer duration of the disease were associated with more steroid consumption and consequently more bone loss, however, this is contrasting the results of Gulati et al. showing that older age at the onset was associated with lower BMD.\textsuperscript{23} The reason seeing these discrepancies is not obvious but it is suggested that lower BMD could be caused by age-related changes in hormonal, calcium and vitamin D metabolism and a more active growth phase.

No difference was found between BMD of femoral and lumbar bones, resulting from the steroid therapy schedules (daily or alternate day). Although this was in concordant to the Polito and colleagues' study who found that alternate day prednisolone therapy did not affect BMC significantly as compared to control group,\textsuperscript{6} but the duration of the disease in their patients was shorter (three yrs) and they used calcium and vitamin D supplements.

In seven patients who received cyclosporine together with steroid, the changes in their bone were not different with those of steroid-treated group. Although, the role of cyclosporine on bone status is still controversial,\textsuperscript{24,25} some reports are in favour,\textsuperscript{24} and the others are against the bone demineralization effect of cyclosporine.\textsuperscript{25}

Conclusion

Bone loss will occur in some patients with steroid-dependent nephrotic syndrome, especially with lower age of onset, longer duration of disease and higher cumulative dose of steroid. Therefore bone mineral density and content measurements are recommended, at least, for selected patients.

References


