Effects of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) on Osteoporosis

Shoji KUMAKI* and Hideki KURIBAYASHI*

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used agents for backache and various joint pains. We suspected that a continuous administration of NSAIDs might suppress bone formation and/or promote bone loss in patients with low bone mineral density (BMD) because the biosynthesis of prostaglandins is inhibited by these drugs. In this study we surveyed the effect of NSAIDs on the bone metabolism in patients with low BMD by comparing a group with NSAIDs administered every day over a period of 1 year and a control group with NSAIDs only occasionally used.

Dual energy x-ray absorptiometry (DXA) was performed on a total of 272 female at our department from April 1999 to September 1999. As a result, 163 cases were found to have BMD less than 80% of the nation’s young adult mean values and considered non-secondary in nature. Out of the 163, we chose 14 cases for the NSAID group, and 51 cases for the control group.

The average age, height and body weight were 73.6 years, 149.1cm and 52.1kg for the NSAID group and 71.7 years, 146.7cm and 48.0kg for the control group. There were no statistical differences in all these items. For the treatment of low BMD, 64.9% of the patients in the NSAID group and 52.9% in the control group had anti-osteoporotic medication. In the NSAID group, the relative changes in BMD between the values of the first measurements and those after a 1-year interval were 2.7% decrease at 2nd lumbar vertebra (L2), 12.4% decrease at 3rd lumbar vertebra (L3), 3.9% decrease at 4th lumbar vertebra (L4) and 4.4% decrease at 2nd – 4th lumbar vertebra (L2 – 4). In the control group these were at each site 2.9% increase, 3.6% increase, 2.3% increase and 2.8% increase, respectively. In the NSAID group, BMD changes at neck, Wards, trochanter and shaft of the femur were 3.6% decrease, 4.6% decrease, 4.2% decrease and 3.9% decrease, respectively in the control group, they were 1.0% decrease, 2.2% increase, 1.6% increase and 0.1% increase, respectively. A comparison between the two groups showed that the percent changes in BMD of L3, L2 – 4, Wards, trochanter and shaft of the femur were statistically significant in the NSAID groups.

The present data suggest that the regular use of NSAIDs enhances bone loss in patients with low bone density detected by DXA examination.

①Bone mineral density ②Osteoporosis ③Nonsteroidal anti-inflammatory drugs (NSAIDs)

Introduction

Nonsteroidal anti-inflammatory drugs, NSAIDs, are one of the most commonly used drugs for backache and various joint pains.
We have a suspicion that NSAIDs may suppress bone formation and promote bone loss in patients with low bone density because NSAIDs inhibit prostaglandin production in the body, leading to a decreased rate of bone formation.

In this study, we tried to detect the effect of NSAIDs on the bone metabolism in patients with low bone density.

We have compared two groups over a period of 1 year: one, a group of patients with low bone density to whom NSAIDs were administered regularly and the other, a control group of patients with low bone density to whom NSAIDs were dispensed only occasionally.

**Subjects and Method**

In our department from April 1, 1999 to September 24, 1999, 272 female patients were examined by dual energy x-ray absorptiometry (DXA) to measure bone mineral density (BMD) either at the lumbar vertebrae or the proximal femur. Of these, 163 cases had non-secondary low BMD less than 80% of the young adult mean values at either the second to fourth vertebrae (L2–4) or the proximal femur.

Out of the 163, we selected for the NSAID group, 14 cases to whom NSAIDs (diclofenac sodium, 5 cases; loxoprofen sodium, 3 cases; nabumetone, 2 cases; etodolac, 2 cases; zoltoprofen, 2 cases; ampiroxica, 1 case; and alminoprofen, 1 case) had been administered every day and had been followed up over 1 year.

For the control group, we chose 51 cases to whom NSAIDs were not given at all or only occasionally over the same period.

For the measurement of BMD, the DXA apparatus (Expert 2000, lunar company, USA) was used. The bone density of each lumbar vertebra from the second to fourth was measured separately and synthesized for combined area if necessary. In the proximal femur, bone density was measured by deviding the interest area into four parts, which are designated the “neck”, “Wards”, “trochanter” and “shaft” in the Expert 2000 BMD report. The value of BMD in Wards is the computer calculated minimal density figure about the certain square area in the neck, which is not geographically equivalent to Ward’s triangle of the femoral neck (Fig. 1).

In addition to BMD data, we compared two groups in terms of age, height, body weight, and activity of daily living (ADL) for the fundamental subject profile. For the assessment of ADL, activity levels were graded into five categories: grade 1, bed-ridden; grade 2, limited to indoor activity; grade 3, occasional outdoor activity, but mainly inside; grade 4, outdoor activity possible but only in the neighborhood; grade 5, possible to take a walk around the neighborhood; grade 6, no limit to outdoor activity.

For statistical analysis concerning all the parameters of BMD, percent changes in each item over the length of 1 year were compared. The difference between the values in each item was compared by Student t-test. Statistical differences of ADL were analyzed by the Mann-Whitney U-test. P<0.05 was considered significant. All values were expressed as

![Fig. 1 Sites of BMD measurement](image-url)
“mean (range).”

**Results**

**The characteristics of the patients**: The subjects were all female, and ages of the two groups were 73.6 (63–81) years for the NSAID group, and 71.7 (57–87) years for the control group with no significant difference. The average height and body weight for the NSAID group were, 149.1 (142–158) cm and, 52.1 (41–73) kg, and for the control group, 146.7 (127–157) cm and 48.0 (33–64) kg, with no significant difference for each item between the two groups (Table 1).

**Assessment of ADL**: In the NSAID group there were three grade 3s, and 11 grade 5s. In the control group there were one grade 1, three grade 2s, six grade 3s and 34 grade 5s. The Mann Whitney U-test analysis showed no significant difference (P = 0.174).

**Table 1** Characteristics of the Patients

<table>
<thead>
<tr>
<th></th>
<th>NSAIDs group</th>
<th>Control group</th>
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<tbody>
<tr>
<td>n</td>
<td>14</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>gender</td>
<td>female</td>
<td>female</td>
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<tr>
<td>age (years)</td>
<td>73.6 (63–81)</td>
<td>71.7 (57–87)</td>
<td>0.37</td>
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<tr>
<td>height (cm)</td>
<td>149.1 (142–158)</td>
<td>146.7 (127–157)</td>
<td>0.21</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>52.1 (41–73)</td>
<td>48.0 (33–64)</td>
<td>0.11</td>
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</table>

**Medical treatment for low BMD patients during the study period**: In the NSAID group, 10 of the 14 patients were dispensed for the treatment of low BMD. Vitamin K2 in seven cases, etidronate in two cases, and calcitonin in one case. In the control group, 27 of the 51 patients were taking medications, vitamin K2 in 13 cases, etidronate in 10 cases, and alfacalcidol in four cases.

**Relative percent changes of BMD**: The relative percent changes in BMD of the lumbar spine during the study period were, in the NSAID group, 2.7 (–12.6 ~ +11.5)% decrease in L2, 5.9 (–21.3 ~ +4.5)% decrease in L3, 3.9 (–22.3 ~ +17.9)% decrease in L4 and 4.4 (–13.9 ~ +11.5)% decrease in L2 – L4. In the control group, these were at each site, 2.9 (–22.9 ~ +26.7)% increase, 3.6 (–16.7 ~ +25.3)% increase, 2.3 (–19.6 ~ +29.0)% increase and 2.8 (–11.9 ~ +18.5)% increase, respectively. The differences in percent changes in L3 and L2 – L4 between the two groups were statistically significant (Table 2).

Changes in the proximal femur in the NSAID group, were 3.6 (–12.4 ~ +3.8)% decrease in neck, 4.6 (–16.8 ~ +15.1)% decrease in Wards, 4.2 (–13.1 ~ +4.3)% decrease in trochanter, and 3.9 (–10.9 ~ +1.0)% decrease in shaft. In the control group, they were 1.0 (–7.5 ~ +8.0)% decrease, 2.2 (–15.5 ~ +28.2)% increase, 1.6 (–14.1 ~ +39.7)%

**Table 2** Rate of Change in Lumbar BMD/year

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<th></th>
<th>NSAID group</th>
<th>Control group</th>
<th>p</th>
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<tbody>
<tr>
<td>L2 BMD</td>
<td>–2.7% (–12.6 ~ +11.5)</td>
<td>+2.9% (–22.9 ~ +26.7)</td>
<td>0.064</td>
</tr>
<tr>
<td>L3 BMD</td>
<td>–5.9% (–21.3 ~ +4.5)</td>
<td>+3.6% (–16.7 ~ +25.3)</td>
<td>0.0026*</td>
</tr>
<tr>
<td>L4 BMD</td>
<td>–3.9% (–22.3 ~ +17.9)</td>
<td>+2.3% (–19.6 ~ +29.0)</td>
<td>0.054</td>
</tr>
<tr>
<td>L2–L4 BMD</td>
<td>–4.4% (–13.9 ~ +11.5)</td>
<td>+2.8% (–11.9 ~ +18.5)</td>
<td>0.0019*</td>
</tr>
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*P < 0.05 significant decrease
increase, and 0.1 (-9.2 ± 9.6)% increase, respectively. The differences in MMD changes between the two groups were statistically significant in neck, Wards, trochanter and shaft of the femur (Table 3).

**Discussion**

Not a few people suffer from osteoporosis-related fractures of the spine, forearm, shoulder, hip, etc.2,3), as the number of osteoporotic patients increases rapidly worldwide. Hip fracture is crucial because of risks of ADL deterioration, the high cost of treatment including surgical operation, and occasional fatalities4). We previously reported the critical levels of bone densities for hip fractures5, where we proposed the cut-off levels for hip fractures,

- neck BMD 0.600g/cm² (sensitivity 76%, specificity 80%)
- Wards BMD 0.400g/cm² (sensitivity 71%, specificity 81%).

There are many causes and reasons for bone fragility in the elderly. The results of the present study suggest that a long-term use of NSAIDs by the patients with musculoskeletal pain can be an adverse factor for the bone metabolism.

Many studies implicate that the inhibition the synthesis of prostaglandins by NSAIDs in the body, particularly prostaglandin E2 in the bone tissue, modulates the remodelling process of bone. Raisz reported in 1977 for the first time that prostaglandins exerted marked resorption effect on the bone tissue in rats6). However, Chambers in 1985 claimed that the agents depressed the rate of resorption by osteoclasts in vivo experiment7). Sudmann et al. in 1979 showed that indomethacin given for only 1 week could inhibit fracture healing in rats8). Several studies on the effect of NSAIDs, such as ibuprofen9), indomethacin10,11) and naproxen12) for the prevention of the heterotopic ossification after hip arthroplasty imply that prostaglandins enhance bone formation. In the report published by P. Gebuhr 1991 concerning the inhibitory effect of NSAIDs against heterotopic ossification after hip arthroplasty, he suggested that all nonsteroidal anti-inflammatory agents have the same efficacy against heterotopic bone formation12). Saino, in 1997, published data of a long-term injection of indomethacin to ovariectomized rats13), which revealed the marked inhibitory effect on bone formation in vivo: the repeated intramuscular loads of indomethacin 15.0mg/kg/week for 24 weeks to the rats reduced the lumbar BMD by 12.5%, trabecular bone moss by 65.5% and trabecular thickness by 32.8%, and so in a dose-dependent manner.

<table>
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<th>Table 3</th>
<th>Rate of Change in Prox Femur BMD/year</th>
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<tr>
<td></td>
<td>NSAID group</td>
</tr>
<tr>
<td>neck BMD</td>
<td>-3.6%</td>
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<tr>
<td></td>
<td>(-12.4 ± 3.8)</td>
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<tr>
<td>Wards BMD</td>
<td>-4.6%</td>
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<td></td>
<td>(-16.8 ± 15.1)</td>
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<tr>
<td>trochanter BMD</td>
<td>-4.2%</td>
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<td></td>
<td>(-13.1 ± 4.3)</td>
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<tr>
<td>total BMD</td>
<td>-3.9%</td>
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<td></td>
<td>(-10.9 ± 1.0)</td>
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*P < 0.05 significant decrease
that the inhibition of the biosynthesis of prostaglandins by NSAIDs results in the prevention of prostaglandin-dependent bone formation.

The use of NSAIDs is sometimes unavoidable in the control of pain. However, its long and continuous use may deteriorate osteoporosis and cause fractures. The authors think that back pain of the osteoporotic patients due to possible intrinsic micro fracture of the vertebrae\textsuperscript{15} will be controlled without use of NSAIDs by 1–2 week bed rest, setting a back brace, and calcitonin injection\textsuperscript{16} with the alternative non NSAID analgesics like acetaminophen or Neurotropin\textsuperscript{6} for patients with acute pain. Patients with knee pain can be treated with application of knee grip, local administration of NSAIDs via plasters with repeated injection of hyaluroniate into joint space for a few months. It is worthwhile now to think differently both acute and chronic age-related musculoskeletal pain, searching new ways for the painful patients' caring and curing.

**Conclusion**

1. Changes in BMD of lumbar and proximal-femur over a 1-year period were compared between 14 patients with NSAIDs and 51 patients without.
2. No significant differences were noted between the two groups in age, height and weight and ADL.
3. In the NSAID group, BMD of L2 and L2–4 decreased significantly.
4. In the NSAID group, BMD at Wards, trochanteric region, and shaft of the femur dropped significantly.
5. Long-term administration of NSAID may be hazardous.
6. Osteoporotic patients should be treated with minimal use of NSAIDs.

**References**

13) Saino H, Matsuyma T, Takada J, et al. Long-term treatment of indomethacin reduces verte-
消炎鎮痛剤の骨密度への影響
——消炎鎮痛剤は骨密度を低下させるか？——

熊木昇二*，栗林秀樹*

消炎鎮痛剤（以下 NSAID）は腰痛や関節痛などを和らげ目的で広く用いられている。しかしNSAIDはプロスタグランジン（以下 PG）の生産を抑制するため、長期に使用すると、PG の骨形成作用が阻害され、骨密度（以下 BMD）が低下する可能性がある。われわれは、低骨量症例の1年間の BMD の変化を調べることで、NSAID の骨密度への影響を調査した。

【対象と方法】99年4月1日から9月24日までに当科でDEXA法による腰椎と大腿骨近位部の BMD を調べ、L2−4 BMD か大腿骨頚部 BMD のいずれかが若年成人平均値の80％以下で続発性でなかった症例は163例であった。この中で NSAID を1年間にわたり投与され、その間の BMD の変化を観察できた14例を対象とした（NSAID 群）。コントロールとして、NSAID を定期的に投与されず、1年間にわたって BMD の変化を観察できた51例を用いた。この2群において、各測定と大腿骨近位部 BMD の1年間の変化率を求め比較検討した。

【結果】両群とも全例女性であり、年齢、身長、体重において有意差を認めなかった。1年間の BMD の変化率で両群を比較すると、まず腰椎では、NSAID 群で L3 BMD、L2−4 BMD が有意に低下し、L2 BMD、L4 BMD が低くなる傾向を認めた。大脛骨近位部では、NSAID 群でWards BMD、troch BMD、total BMD が有意に低下し、neck BMD が低くなる傾向を認めた。

【結論】NSAID を長期に使用すると、骨密度が低下する可能性が示唆された。

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