DECREASED MANDIBULAR BONE MINERAL DENSITY IN ADULTS WITH FAMILIAL MEDITERRANEAN FEVER

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ABSTRACT

Introduction: Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by attacks of fever and serositis. Patients with FMF may use a lot of medications associated with the clinical symptoms. Drugs that are used in the treatment of FMF may cause bone loss. The aim of this study was to define mandibular bone mineral density (BMD) in adults with FMF using dual energy X-ray absorptiometry (DXA) technique.

Materials and methods: The study comprised 28 patients diagnosed with FMF (male/female: 16/12), and 32 healthy control subjects (male/female: 18/14) with no history of inflammatory disease. The BMD of each mandible was measured by DXA.

Results: There was no statistically significant difference in gender, age or body mass index (BMI) between the FMF patients and the control group but mandibular BMD was significantly decreased in patients with FMF.

Conclusion: However, it is difficult to draw any conclusions from the current cross-sectional study, FMF were found to be associated with decreased mandibular bone density. The results of the present study revealed that the mandibular BMD level was lower in FMF patients than in the control group.

Key words: Familial mediterranean fever, bone density, mandible, dual energy X-ray absorptiometry.

DOI: 10.19193/0393-6384_2016_2_61

Received May 30, 2015; Accepted January 02, 2016

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive hereditary disorder and is generally seen in certain ethnic groups such as Sephardic Jews, Armenians and Arabs. Geographically, the disease is more commonly observed among the nations of the Mediterranean region. The prevalence of the FMF varies among 1:150 - 1:73,000 according to the ethnicity. The disease has an estimated prevalence of 1/1000 in Turkey, and the carrier rate is 1:5. With regard to gender, FMF is more common in men than in women, the male to female ratio is 2:1.

FMF has two typical clinical periods, which are inflammation (attack period) and remissions (attack free period). Patients have an increased acute-phase response in attack periods and usually returns to normal in attackfree periods. FMF is characterized by recurring short episodes of a high-grade fever, abdominal pain and cutaneous, serosal, or synovial inflammation. In 90% of cases, these symptoms occur before the age of 20 years. Mutations in the Mediterranean fever gene (MFV) causes FMF, which is located on chromosome 16. The MFV gene is encoded by pyrene protein. This is a protein which controls inflammation in a healthy process but when a mutation develops in the MFV gene, the mutation causes the inflammation process to be out of control by preventing the encoding of pyrene.

The increased inflammation associated with an uncontrolled inflammatory process may lead to many adverse effects, such as body structure and
growth distortion with poor bone development. Many studies have shown that ongoing inflammation has adverse effects on bone mineral density (BMD) and causes retarded growth and development. Although FMF has variable attacks, it is rare for there to be long periods of immobility that could cause osteoporosis. However, some studies have shown that subclinical inflammation may affect the continuity of bone metabolism between attacks of FMF. This has been stated to be associated with cytokines, which are crucial mediators of inflammatory responses, and have a significant role in the organization of bone formation and resorption during pathological bone remodeling.

Therefore, it has been suggested that osteoporosis may occur in FMF patients. Various authors have described decreased BMD in FMF patients, although there are conflicting results in literature with other studies reporting that FMF had no effect on BMD. There have been few systematic studies carried out to date.

The complex relationship between oral bone loss and systemic osteoporosis is of great interest to many clinicians and researchers. It is suspected that a systemic component contributes to the loss of teeth, periodontal tissue, and mass of the alveolar bone but this has not yet been fully elucidated. There have been mixed results from human studies attempting to relate systemic measures of BMD to oral measures of bone health using radiographic techniques.

The density of the jaw bone is a significant factor in contemporary dental treatment planning and management of dental processes such as dental implant osseointegration, bone grafting and periodontal treatment. Where there is any question of systemic inflammatory disease, such as FMF, affecting BMD, the possibility of bone loss in the jaw during a dental procedure becomes highly significant. Currently, the most appropriate method for quantifying BMD is dual energy X-ray absorptiometry (DXA). Previous clinical studies in literature have reported the use of DXA to measure mandibular BMD. In several studies lumbar and femoral BMD have been investigated in patients with FMF and varying prevalence and degrees of osteopenia or osteoporosis have been shown.

However, to the best of our knowledge, the effect of FMF on mandibular BMD has not been previously assessed. The primary aim of this study was to determine mandibular BMD values in patients with FMF and to evaluate these in the light of current literature. The secondary objective of the study was to compare the mandibular BMD values of the FMF patients with those of a healthy control group.

Materials and methods

Study population

The study participants were composed of two groups:

Group A (FMF Group): 28 adults with FMF (male/female: 16/12);

Group B (Control Group): 32 healthy adults (male/female: 18/14).

The diagnosis of FMF was established according to previously described criteria in the Department of Medical Genetics, Faculty of Medicine, Afyon Kocatepe University. All FMF patients were in an attack-free period and all were receiving 1-1.5 mg/day of colchicine therapy. The healthy subjects were randomly chosen from volunteer patients in the Department of Oral and Maxillofacial Surgery and the Department of Periodontology, Faculty of Dentistry, Afyon Kocatepe University, who had received a dental examination as part of their routine dental treatment. The Ethics Committee of Afyon Kocatepe University Faculty of Medicine granted approval for the study.

Exclusion criteria

Patients who had been previously diagnosed as having any systemic disease other than FMF or who were currently using drugs that could affect BMD were excluded from the study. Using DXA, BMD measurements of the lumbar spine (L1-L4) were taken followed by BMD measurements of the mandible. T scores between -1 and -2.5 were considered to indicate osteopenia, and scores ≤ -2.5 were considered to indicate osteoporosis. These osteopenic and osteoporotic patients were excluded from study. Further exclusion criteria were the presence of considerable infection or bone pathology (cysts, tumors), absence of all premolars and molars in the mandible and edentulous mandible

BMD measurement

The BMD (g/cm2) of the mandible was measured using DXA (GE Lunar DPX-NT, LUNAR Corp, Madison, WI). BMD measurements were performed on the corpus mandible as previously described. To avoid superimposition of the cervical vertebrae, the volunteers were laid down on their left side with the neck extended position. Scanning...
of mandibles were started from 2 cm overhead the temporomandibular joint (TMJ) through the corpus of the mandible. Figure 1 shows the scanned image of the mandibular DXA. After the DXA scan, the images were screened on the monitor and region of interest (ROI) placed to the corpus of mandible for BMD measurement. The size of the ROI was adapted to fit to the corpus of the mandible of each patient. The BMD (g/cm²) of the mandible was measured and analyzed by one independent physiatrist who was blind to our study.

**Figure 1**: A sample of jaw scanning for mandibular bone mineral density (BMD) measurement and selection of region of interest on corpus mandible.

**Statistical analysis**

The statistical calculations were made using Statistical Package for the Social Sciences (SPSS) for Windows v. 15.0 software (SPSS Inc., Chicago, IL, USA). To test the normality of the data, the Kolmogorov-Smirnov and Shapiro-Wilk tests were used. For comparisons of groups with normal data distribution, the parametric Student-t test was used. For comparison of gender as a categorical variable, the Chi-square test was used. As the sample number was below 30 in the group comparison according to gender and the distribution was not accepted as normal as there were two groups, the non-parametric Mann-Whitney U-test was applied. The results for the parametric tests were expressed as mean ± standard deviation (SD) and the results for the non-parametric tests were expressed as median and min-max. A value of p<0.05 was considered statistically significant.

**Results**

There was no statistically significant difference in gender, age or BMI between the FMF patient group and the control group (Table 1). A statistically significant difference was observed between the FMF group and the control group in respect of mandibular BMD. When comparisons were made according to gender, statistically significant difference was determined between male FMF patients and male control subjects. Also, a statistically significant difference was determined between the female FMF patients and the female control subjects in respect of mandibular BMD (p<0.05). In all comparisons, FMF patients had decreased BMD than control group patients (Table 2, Figure 2).

**Table 1**: Characteristics of patients according to gender, age and body mass index (BMI).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>FMF Group (n=28)</th>
<th>Control Group (n=32)</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: Female</td>
<td>16:12</td>
<td>18:14</td>
<td>p=0.944</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>33.7±6.98</td>
<td>35.2±6.69</td>
<td>p=0.901</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>26.2±5.05</td>
<td>28.1±4.65</td>
<td>p=0.602</td>
</tr>
</tbody>
</table>

**Table 2**: Mandibular bone mineral density values (g/cm²) according to patient groups and gender.

<table>
<thead>
<tr>
<th>Gender</th>
<th>FMF Group (n=28)</th>
<th>Control Group (n=32)</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>(n=16)</td>
<td>(n=18)</td>
<td>p=0.017</td>
</tr>
<tr>
<td>Median</td>
<td>1.504</td>
<td>1.715</td>
<td></td>
</tr>
<tr>
<td>(Min-Max)</td>
<td>(1.237-1.753)</td>
<td>(1.339-2.043)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>(n=12)</td>
<td>(n=14)</td>
<td>p=0.005</td>
</tr>
<tr>
<td>Median</td>
<td>1.535</td>
<td>1.744</td>
<td></td>
</tr>
<tr>
<td>(Min-Max)</td>
<td>(1.154-1.757)</td>
<td>(1.468-2.376)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>(n=28)</td>
<td>(n=32)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>1.500±0.186</td>
<td>1.737±0.230</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2**: Box-plot diagram of familial Mediterranean fever (FMF) and control group’s mandibular dual-energy X-ray absorptiometry measurements of mandibular bone mineral density (BMD).

**Discussion**

It has been suggested that FMF is a prototype of autoinflammatory diseases. Although inflammat-
ry processes are known to have a major role in the pathology of FMF, the factors that affect inflammation during the attack and attack-free periods require further investigation. Many studies have reported that continuing inflammation decreases BMD\textsuperscript{15-18,39}. Partial explanations have been proposed for the pathogenesis of the bone metabolism found in FMF patients. Firstly, some factors, such as disease activity, loss of appetite, hormonal disorders, decreased mobility and physical activity may lead to decreased BMD at the time of attacks in FMF patients and may also lead to subclinical inflammation\textsuperscript{48}.

Secondly, there is growing evidence to suggest that subclinical inflammation is characterized by elevated levels of proinflammatory cytokines, such as IL-1, sIL-2r, IL-6, TNF-α, IFN-γ, IL-17, and IL-18 during attack-free periods\textsuperscript{6,7,40-44}. Proinflammatory cytokines have a key role in the regulation of bone resorption and formation\textsuperscript{19}. Thus, BMD may be affected as a result of the changes in cytokine levels. In addition, Th1 polarization may result in inflammation in FMF patients in both attack and attack-free periods. Two previous studies have reported increased levels of plasma IFN-γ, which is a Th1-type cytokine, in FMF patients compared to healthy controls\textsuperscript{42,43}.

The validity of the hypothesis that FMF patients may have lower BMD and osteoporosis has been the subject of previous research. In the first study on this topic by Duzova et al.\textsuperscript{18}, a significant decrease in the mean BMD of the lumbar spine was determined in pediatric FMF patients compared with a control group. While most studies have found decreased BMD values in the lumbar spine, femoral neck, proximal femur and total femur in adult patients with FMF\textsuperscript{18,20,34}, there are also other studies which have reported that the lumbar, proximal femur, femoral neck and total femur BMD values in FMF patients were comparable with those of a healthy control group\textsuperscript{22,23}.

These conflicting results may be due to differences in numbers of patients, inclusion/exclusion criteria, and different methodology. However, very few studies in the field of dentistry have investigated the status of FMF patients. To the best of our knowledge, this is the first study evaluating mandibular BMD in adult patients with FMF and comparing the results with healthy control group using the DXA method. The objective of this study was to investigate whether or not there is any change in mandibular BMD in adult FMF patients.

The results of this cross-sectional study demonstrated that FMF patients had significantly lower mandibular BMD values than the control group. The mean mandibular BMD was found to be 1,500±0,186 g/cm2 in the study group and 1,737±0,23 g/cm2 in the control group. The control group values in the present study are similar to the control group values of previous studies. Although there is no study in literature with which a direct comparison can be made, it can be concluded from these results that active inflammatory periods and continuous subclinical inflammation in FMF patients may lead to decreased mandibular BMD.

Current data in literature indicates that subclinical inflammation continues during attack-free periods even if patients are on regular colchicine treatment\textsuperscript{46,47}. Moreover, despite differences in methodology with the above-mentioned studies, the results of the present study are consistent with the vast majority\textsuperscript{18,20,21,34}.

Control group subjects were selected to match the FMF patients in respect of age, sex, socioeconomic status and BMI to increase the comparability and minimize the effects of these parameters on the mandibular BMD measurements. Moreover, patients with any condition that could cause changes in BMD, those using any drugs that could affect BMD and those with any disorder resulting in secondary osteoporosis were excluded from the study. Therefore, the differences in mandibular BMD values between the two groups can be considered to have developed from the inflammatory status of FMF.

Determination of the BMD of the jaw is important in dental procedures such as dental implant application and guided tissue/bone regeneration\textsuperscript{48,53}. As implant procedures have become increasingly common, BMD may be crucial not only in primary implant stability, but also in the estimation of oral implant outcomes. An awareness of the probability of bone loss in the mandible is of great importance in these procedures. Low systemic BMD has been considered as a risk factor for the loss of periodontal attachment and periodontal disease progression\textsuperscript{54}.

Therefore, the possibility of low BMD in FMF patients is a significant factor in the treatment planning, management and prognosis of the surgical and periodontal treatment process. According to the results of this study and the majority of the previous studies in literature, FMF patients have lower BMD levels than healthy individuals. Consequently, den-
tists should be aware of the inflammatory status of FMF patients when planning bone-related surgeries and determining the prognosis of periodontal disease.

Mandibular BMD was measured with the DXA method in the present study. Although bone biopsy is considered to be the “gold standard” measurement of mandibular BMD, it is not possible for ethical reasons and the most appropriate current method for quantifying BMD is DXA\(^\text{17}\). The DXA technique yields non-invasive, fast and highly precise BMD measurements\(^\text{35}\). A significant correlation has also been reported of mandibular BMD evaluated by the DXA method with BMD measurements of whole body\(^\text{56,56}\). Horner K et al.\(^\text{17}\) suggested that corpus of mandible have more sensitivity and specificity than the ramus and the symphysis in detection of osteoporosis. Therefore, in the present study, BMD measurements were performed on the corpus of the mandible. Another important factor in mandibular BMD studies using the DXA technique is superimposition. In the present study, when the required superimposition was obtained, image was recorded for BMD measurement. An ideal superimposition of the mandible was achieved in all subjects.

Standard treatment for FMF is colchicine and all the patients in the current study were using this drug. Colchicine is thought to have a positive effect on bone mineral metabolism. Further case-control studies comparing groups with and without colchicine treatment are required to confirm the effect of colchicine on mandibular BMD, although this would be difficult as it is not ethically acceptable to leave patients without colchicine. Patient groups using different doses of colchicine could be compared with healthy control subjects instead of a colchicine-free group. Another point to consider related to the present study may be the disease duration of FMF. The mean disease duration of the FMF patients in the current study was 5.3 years.

However, a recent study suggested that disease duration does not have an effect on BMD in FMF\(^\text{29}\). Another limitation of the current study could be the small sample size but as the disease has a low prevalence in Turkey, it was not easy to find patients conforming to the strict inclusion/exclusion criteria.

**Conclusion**

The results of the present study revealed that FMF patients had lower mandibular BMD levels than the control group. Decreased mandibular BMD values can be considered to arise from acute inflammatory attacks and subclinical inflammation of the disease. However, it is difficult to draw any conclusions from the current cross-sectional study and further case-control studies are needed to clarify the specific etiology of decreased mandibular BMD in patients with FMF.

However, it can be said that dentists should take into consideration the BMD values and inflammatory status of FMF patients when planning treatment.

**References**

13) Papin S, Cuenin S, Agostini L, Martinon F, Werner S, Beer H, et al. The SPRY domain of Pyrin, mutated in familial Mediterranean fever patients, interacts with inflammasome components and inhibits proIL-1β pro-
Acknowledgements and Conflict of Interest

The authors have no conflict of interest to declare related to this study.

We would like to thank Prof. Dr. İsmet DOĞAN for his support in the statistical analyses.

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