Clinical applications of Dixon chemical shift MR imaging: Morbus Gaucher, Morbus Hansen
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Quantification of skeletal involvement in adults with type 1 Gaucher disease: fat fraction measured by Dixon quantitative chemical shift imaging (Dixon QCSI) is a valid parameter

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**ABSTRACT**

**Objective:**
The objective of this study is to determine the merit of the fat fraction $F_f$ of axial bone marrow measured by Dixon quantitative chemical shift imaging (Dixon QCSI) as a clinical parameter to quantitatively assess the extent of skeletal involvement in type 1 Gaucher disease.

**Materials and Methods:**
Dixon QCSI was performed in 30 untreated adult patients (mean age 39 years [range 18-69 years]) with type 1 Gaucher disease. The relation between the mean value of $F_f$ in the vertebrae L3, L4 and L5 and the presence, absence and the severity of clinical bone complications (chronic bone pain, bone crisis, fracture, avascular necrosis and joint replacement) as well as the conventional MR imaging evaluation of bone marrow involvement were studied. Also the relation of $F_f$ with gender, age and other disease parameters (history of splenectomy, liver and spleen volume, plasma chititriosidase, hemoglobin level and platelet count) was evaluated. Our results were compared to the $F_f$ of healthy volunteers.

**Results:**
The $F_f$ measured in patients with Gaucher disease ranged from 0.08-0.40 (mean 0.20). Bone complications occurred primarily in patients with $F_f$ less than 0.23. Univariate logistic regression analysis indicated that for every decrease of $F_f$ of 0.1 the risk of bone complications increased with 85% ($p<0.05$). $F_f$ was correlated to liver size, but no correlation to other disease parameters was found. In the patient population $F_f$ was significantly lower than in the healthy population (0.27-0.55, mean 0.37) ($p<0.001$).

**Conclusion:**
The fat fraction of the lumbar spine when measured with Dixon QCSI is associated with the occurrence of bone complications. It may therefore be a clinically useful parameter.
INTRODUCTION

Gaucher disease is the most prevalent lysosomal storage disorder, first described in 1882 by the French pathologist Philippe C. E. Gaucher [1]. The non-neuronopathic type 1 variant of the disease is the most common phenotype. The decreased activity of the lysosomal hydrolase, glucocerebrosidase, results in the accumulation of glucosylceramide (glucocerebroside) laden macrophages (Gaucher cells) in liver, spleen and in bone marrow. Bone disease is the most debilitating feature of type 1 Gaucher disease: in almost all patients there is skeletal involvement, ranging from mild osteopenia with minimal symptoms to major bone disease such as bone infarcts, osteonecrosis or fractures [2-7].

MR imaging is the imaging modality of choice for the evaluation of the extent of bone marrow disease due to its excellent soft tissue contrast and its sensitivity for the detection of both focal and diffuse disease [8-13]. The striking features of Gaucher disease infiltration on MR imaging are the focal or diffuse low signal intensity both on T1- and T2-weighted sequences in the bone marrow of the axial and peripheral skeleton [9-11]. The epiphyses of the long bones are relatively spared in mild disease and their infiltration is thought to represent severe Gaucher disease [9-11]. Areas in the bone marrow with high signal intensity on T2-weighted images are considered to represent acute disease [10].

Quantification of bone marrow involvement has become increasingly important in clinical management, both for the purpose of determining eligibility for therapy and for therapy monitoring, as the currently used enzyme supplementation therapy is very costly. For this purpose Dixon quantitative chemical shift imaging (Dixon QCSI) of the lumbar spine has been investigated [4,10-12,14]. This non-invasive technique is based on the phase contrast technique described by Dixon [15], in which the MR imaging signal is separated into the individual contributions of fat signal and water signal [12]. In this way the amount of fat can be quantified, and is represented as a fat-fraction \( F_f \) [4,10-12,14]. Evidence has been presented that infiltration of bone marrow in Gaucher disease causes a decrease of \( F_f \) since the total mass of lipid is less than normal because of displacement of triglyceride-rich adipocytes by Gaucher cells [3,4,13,14]. These data support a model of a dynamic process of bone marrow alterations in which \( F_f \) is inversely correlated with the amount of Gaucher
cells in the bone marrow, thus reflecting severity of bone marrow involvement [4,11,12,14].

The use of \( F \) as a parameter for Gaucher disease invasion is recognized among researchers and clinicians. Also the excellent reproducibility of this technique has recently been addressed [16]. Since \( F \) is a bone marrow parameter it may be useful as parameter of bone disease. This would be very convenient since a validated dynamic bone disease parameter is currently not available in the management of Gaucher disease.

The goal of this study is to validate lumbar \( F \) as a quantitative overall bone disease parameter. Therefore the relation of lumbar \( F \) with the presence and the clinical extent of skeletal disease is analyzed. Also the value of \( F \) as a prognostic parameter for bone disease is studied by calculating the relative risk. Furthermore \( F \) in healthy volunteers is compared to the data from the Gaucher population. In addition the correlation of \( F \) with the degree of organomegaly and cytopenia, as a measure of visceral and hematological involvement of Gaucher disease, is studied.

**Materials & Methods**

*Patients & Volunteers*

This study was performed in a University Hospital setting, a national referral center for Gaucher disease [17], between July 1993 and June 1998. We consecutively included untreated adult patients with type 1 Gaucher disease, who were referred for evaluation of eligibility for treatment. All patients underwent Dixon QCSI analysis as part of the diagnostic work-up that also includes MR imaging of the lumbar spine and the femur [18]. The measurement of glucocerebrosidase activity in leukocytes and genotyping was used to confirm the diagnosis of Gaucher disease in all patients [19-21]. The data from healthy volunteers were reported in a previous study in which the reproducibility of Dixon QCSI as a technique of measuring the \( F \) of bone marrow was evaluated [16].

*Dixon QCSI fat-fraction of the axial skeleton*

In-phase and opposed-phase proton density weighted spin echo sequences were performed on a 1.5 T magnet (Magnetom SP4000 and Vision, Siemens, Erlangen, Germany) with the following parameters: TR
2500 ms, TE 22.3 ms, slice thickness 4 mm, matrix 256x256, number of excitations 1, field of view 350x350 mm². The coronal measurement acquisition slices were positioned on a mid-sagittal localizer image, passing through the middle of the posterior parts of L3, L4 and L5, as illustrated in Figure 1 [16]. The direction of the measurement slice was selected with care to avoid motion artifacts.

![Figure 1](image-url)

**Figure 1.** 35-year old healthy male volunteer in whom placement of measurement slice and determination of region of interest (ROI) is illustrated. **a.** Measurement slice is indicated on a mid-sagittal localizer image; it is perpendicular to localizer image and it passes through junction of the anterior three-quarter with the posterior one-quarter of vertebral body L4. Angulation from coronal towards transversal is applied to make slice pass optimally through the posterior parts of L3 and L5. **b.** In coronal in-phase magnitude image the vertebrae are clearly distinguishable from their surroundings. **c.** Interactively, with help of a mouse, the contours of vertebrae L3, L4 and L5 are drawn. **d.** By applying four erosion operations to the interior region of the contours, the ROIs are obtained in coronal plane.

Post-processing and data analysis were performed on a Sun Sparc 20-51 workstation (Sun Microsystems, Mountain View, CA), using a previously described algorithm [22,23]. To obtain one fat-fraction value for each vertebra, we averaged the pixel values over a user-defined region of interest (ROI). This ROI covered all but the peripheral edges of the vertebral bodies, thus avoiding inclusion of reactive changes due to
Chapter 4

degenerative disc disease and avoiding partial volume averaging (Fig. 1). The mean $F_r$ of the three vertebrae L3, L4 and L5 was used as overall $F_f$.

Clinical assessment of bone disease
The clinical signs related to severity of skeletal disease in Gaucher disease were assessed as follows: the presence of a history of bone complications was recorded for each patient. To analyze the relation between the severity of skeletal disease and $F_r$ we clinically subdivided bone complications in the presence or absence of either of the following: chronic bone pain, bone crisis, fracture, avascular necrosis and joint replacement. If a fracture, avascular necrosis or a joint replacement was present the complications were considered to be severe. If only bone pain or a history of a bone crisis was present, then the complications were considered to be mild. Also the gender of the patients was analyzed, since male gender is described as a risk factor for osteonecrosis [7].

Radiological assessment of bone disease by conventional MR imaging
The radiological involvement of bone marrow was assessed using conventional MR imaging of the peripheral skeleton as described previously [5,11]. The scoring system is based on the fact that Gaucher disease spreads centrifugally starting from the diaphysis. The infiltration of the femoral diaphysis was scored as 1 point, the infiltration of the proximal epiphysis/apophysis was scored as 2 points and the infiltration of the distal epiphysis of the femurs was scored as 3 points.

Other clinical and laboratory parameters
The history of splenectomy was recorded. The exact volumes of liver and spleen were measured with the use of helical-CT with a method described earlier [17]. Plasma chitotriosidase levels served as a marker for total visceral Gaucher cell burden [24]. As hematological parameters the hemoglobin levels and platelet counts were determined.

Data analysis and statistics
Data were analyzed using SPSS 10.0 software (SPSS, Chicago, Illinois). Differences between groups were tested using the non-parametric Mann-Whitney test. A $p$-value of less than 0.05 was considered to represent significance. Correlation was calculated using the two-tailed non-parametric rank correlation (Spearman’s $\rho$).
Furthermore a univariate logistic regression analysis was performed in order to analyze $F_r$ as a bone disease parameter for the prediction of the relative risk. For this purpose the $F_r$ was subdivided in categories of 10% fat-fraction.

**RESULTS**

*Patients & Volunteers*

A total number of 30 consecutive adult type 1 Gaucher disease patients were included. One patient was diagnosed with an additional bone marrow disorder; multiple myeloma and therefore was excluded from this study. This leads to 29 patients for further analysis, 16 men, 13 women, with a mean age 40 years (range 18-69 years).

**Table 1.** List of the 9 patients with their fat-fractions and bone complications.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Fat fraction</th>
<th>Chronic bone pain</th>
<th>Bone crisis</th>
<th>Pathological fracture</th>
<th>Avascular necrosis</th>
<th>Joint replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>M</td>
<td>0.11</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>F</td>
<td>0.11</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>F</td>
<td>0.19</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>M</td>
<td>0.10</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>M</td>
<td>0.12</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td>F</td>
<td>0.16</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>M</td>
<td>0.34</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>36</td>
<td>M</td>
<td>0.22</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>36</td>
<td>F</td>
<td>0.08</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Nine patients had a clinical history of bone disease of which six had severe bone disease (Table 1). Of these nine patients seven patients were splenectomized. The total number of patients with a splenectomy was nine.
The healthy volunteers group consisted of eight men and eight women: mean age 39 years (range 24-60 years).

*Fat fraction, $F_f$*

The fat-fractions measured in Gaucher disease patient's vertebral marrow ranged from 0.08-0.40 (mean 0.20). The value of $F_f$ in the healthy population ranged from 0.27-0.55 (mean 0.37). The difference between the groups was statistically significant ($p<0.001$) (Fig. 2). In Figure 3 the distribution of $F_f$ amongst the various subgroups is shown. No significant relation was found between fat-fraction and age ($p=0.12$). No statistical significant difference between men and women was found ($p=0.88$).

![Figure 2. Plot of fat-fraction $F_f$ for healthy volunteers and Gaucher disease patients.](image)

*Skeletal disease and $F_f$*

When analyzing the relation between clinical bone complications and fat-fraction it is noted that eight out of nine patients with bone complications had an $F_f$ less than 0.23. In order to analyze the relation between $F_f$ and bone complications a univariate analysis was performed. (The outlier was excluded in this analysis.)
This univariate logistic regression analysis showed that increase of 10% of the fat-fraction meant a decrease in the relative risk for developing bone complications by 85% (\( p < 0.05 \)). The radiological skeletal involvement measured by conventional MR imaging (in the healthy volunteers scored as zero) showed a significant inverse correlation with \( F_f \) (\( \rho = -0.78, p < 0.001 \)). Also a relation was established between the MR imaging score and the occurrence of bone complications (\( \rho = 0.58, p < 0.001 \)).
In general a lower $F_r$ was found in splenectomized patients; this was nearly significant compared to the non-splenectomized group ($p=0.06$). The inverse relation between $F_r$ and the volume of the liver is significant ($p = -0.77, p<0.0001$) but did not reach significance for the volume of the spleen ($p = -0.52, p=0.79$). In a univariate analysis the occurrence of bone complications was significantly associated with the presence or absence of the spleen ($p=0.002$) and with platelet count ($p=0.01$) (higher risk for bone complications in patients without a spleen and with a high platelet count). These two parameters are obviously related to each other. Pancytopenia in splenectomized patients may reflect bone marrow infiltration and is therefore possibly related to $F_r$. However, only four of nine splenectomized patients showed slightly decreased hemoglobin levels and/or platelet count. In these splenectomized patients, no relation was established between $F_r$ and these parameters. The relation between chitotriosidase levels and $F_r$ did not reach significance.

**Discussion**

This is the first report that describes in an adult untreated population of Gaucher patients a close relationship between the extent of skeletal disease and a quantitative secondary parameter, that is, lumbar bone marrow fat-fraction. The presented detailed comparison of lumbar $F_r$ and both clinical and radiological (MR imaging) skeletal disease suggests that lumbar $F_r$ may be a sensitive predictor of ongoing skeletal disease in Gaucher disease patients. The fact that $F_r$ correlates well with the peripheral MR imaging score, a parameter that is known to detect response to therapy [14], suggests that $F_r$ potentially is a sensitive quantitative parameter for the evaluation of skeletal response to enzyme supplementation therapy.

This study has revealed that Dixon QCSI as assessed with MR imaging in Gaucher patients significantly relates the extent of mainly peripheral bone disease to the axial lumbar bone marrow fat-fraction $F_r$. Bone complications preferentially occurred in patients with an $F_r$ less than 0.23. In a univariate logistic regression analysis, we established a further relationship between $F_r$ and the risk for the occurrence of bone complications: when $F_r$ decreases with 10%, the relative risk of developing
bone complications increases with 85% ($p<0.05$). This analysis is limited by the small sample size and the lack of longitudinal data. Nevertheless we feel that based on these data, the patients in the Gaucher disease group with a low $F_f$ without bone complications are considered at risk. This is in concordance with an earlier observation made by Rosenthal et al. [11], when they described that marrow infiltration and replacement by Gaucher cells can remain silent for a long period of time before the appearance of clinically significant bone disease. This relation between low $F_f$ and relative risk on bone complications is further supported by the observation made during follow-up. The two patients that suffered from bone complications during enzyme therapy had a low $F_f$ at baseline and showed no or minor improvement in $F_f$ during therapy [25, Hollak unpublished data]. The correlation that was suggested between low $F_f$ and the development of bone complications but could not be proven earlier is supported in our study. Furthermore a significant difference was found in mean $F_f$ between Gaucher disease patients and healthy volunteers.

In our data there is one patient that does not follow the trends. This patient is an outlier in fat-fraction as well as liver volume, but not in genotype (N370S/L444P). It is very difficult to find an explanation for this. The fact that he is the only patient who suffered from a bone crisis some weeks prior to the QCSI measurements may influence the local bone marrow composition and therefore the fat-fraction. However there is no literature data to support this.

Two other studies have reported on lumbar $F_f$ in untreated type 1 Gaucher disease patients. Johnson et al. [4] performed Dixon QCSI measurements in 24 patients. Their $F_f$ ranged from 0.006-0.32, with a mean of 0.10. Rosenthal et al. [14] studied 12 patients with type 1 Gaucher disease using Dixon QCSI; their $F_f$ ranged from 0.006-0.26 with a mean of 0.073. Compared to these data, the present $F_f$'s are higher, suggesting that our patient population was less severely affected. An additional explanation for the difference may be the age difference. In the two studies mentioned, a considerable number of children and adolescents were included. The younger, healthy age groups will intrinsically show a lower $F_f$, because of the predominant presence of red cellular marrow in their axial skeleton [26]. During adolescence a marked conversion of red to fatty marrow occurs, resulting in a dynamic increase
in $F_r$ values [8,25-28]. Thus in a person of younger age a measured low fat-fraction may be the sum of Gaucher disease infiltration and the presence of more red marrow. This study is the first study that compared the distribution the lumbar $F_r$ of adult type 1 Gaucher disease patients to the distribution the lumbar $F_r$ of adult controls with a comparable age distribution. The lumbar $F_r$ of adult type 1 Gaucher disease patients is significantly reduced.

In two other reports Dixon QCSI data, MR imaging scores and skeletal disease manifestations are comparatively discussed [7,13]. Rodrique et al. [7] did not find the fat-fraction to be a significant determinant for the occurrence for osteonecrosis. However, correlation of lumbar $F_r$ with less severe manifestations of skeletal disease was not evaluated in that particular study. In the study by Rosenthal et al. [14] the MR score of the peripheral skeleton and the fat-fraction measured by QCSI were analyzed as response parameter to therapy. The relationship between fat-fraction and conventional MR imaging score however was not analyzed.

There are a few limitations to consider. First one must realize that QCSI is not a standard sequence on an MR imaging machine and therefore not widely available. Thus the fat-fraction as such is not a parameter that is used worldwide. A limitation of this particular study, like in almost every paper concerning Gaucher disease, is the small number of patients that are included. In this way the statistical evaluation is hampered.

In Gaucher disease it is striking that the various parameters that monitor the possible sites of involvement such as organ volume, platelet count and history of skeletal disease show a poor correlation [4,7,14]. Although a significant correlation between $F_r$ and liver volume was found in this study, this was not found with splenic volume. The Gaucher burden in liver and spleen does not necessarily predict the burden of Gaucher disease in bone marrow; there may be a considerable individual variation in the extent of involvement of visceral and bone marrow compartments. This could implicate that non-skeletal parameters will not adequately reflect skeletal or bone marrow involvement adequately and emphasizes the need for adequate separate quantitative assessment of bone marrow to allow overall interpretation of disease severity.
In summary, to answer the goals of our study we can conclude that fat-fraction measurements through the use of Dixon QCSI showed a close correlation with the clinical occurrence of skeletal involvement. There was a significant difference between the fat-fractions in untreated Gaucher disease patients when compared to healthy volunteers. Finally the fat-fraction may serve as a prognostic marker since univariate regression analysis showed that the decrease in fat-fraction with 10% is associated with an increased risk for occurrence of bone complications by 85%. Only a longitudinal study in patients under treatment can prove its value in clinical decision-making and outcome. In our view it is essential for optimal patient care to monitor the skeletal involvement on a regular basis and Dixon QCSI seems a valuable tool.

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