Clinical applications of Dixon chemical shift MR imaging: Morbus Gaucher, Morbus Hansen
Maas, M.

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Imaging and Quantifying Skeletal Involvement in Gaucher Disease

M. Maas¹, L.W. Poll², and M.R. Terk³

Department of Radiology¹, Academic Medical Center, Amsterdam, The Netherlands; Institute of Diagnostic Radiology², Heinrich Heine University, Düsseldorf, Germany; and Keck School of Medicine³, University of Southern California, USA

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ABSTRACT
Radiological imaging is used in patients with Gaucher disease to estimate the disease burden, to evaluate the presence of specific skeletal complications, and to track response to therapy. MRI is currently the best technique for assessing bone marrow involvement in Gaucher disease. Gaucher cell infiltrated bone marrow is characterized by an abnormal low signal intensity on conventional T1- and T2-weighted spin echo sequences, owing to a reduction in fat marrow, which gives a high signal intensity. Enzyme replacement therapy results in a degradation of Gaucher cell deposits with a reversion of marrow fat and consequently an increased signal on T1-weighted images. Conventional MRI also detects other skeletal complications in Gaucher disease, including oedema resulting from acute bone infarction, infection and trauma, avascular necrosis, pathological fractures, and vertebral compression. The main drawback of conventional MRI is that it is not quantitative. Quantitative chemical shift imaging is the most sensitive quantitative method for evaluating bone marrow but is not widely available. Alternative MRI-based methods include calculation of the T1 relaxation constant and proton spectroscopy. Scoring of imaging changes detected on conventional MRI may be useful in estimating disease burden and risk of complications. Dual-energy X-ray absorptiometry (DXA) is sensitive to generalized osteopenia and changes in bone mineral density with extended enzyme replacement therapy. However, DXA is insensitive to local changes and cannot yet be used to predict fracture risk in these patients. Until the ideal quantitative technique is developed, conventional MRI will remain the best diagnostic modality for assessing skeletal complications in Gaucher disease and monitoring response to enzyme replacement therapy.
INTRODUCTION

In Gaucher disease, accumulation of Gaucher cells in the bone marrow triggers a series of events that lead to skeletal pathology. Skeletal involvement is seen on radiography in nearly all patients [1,2] but is not always associated with symptoms. When skeletal symptoms occur they can be totally debilitating [3].

The severity of bone involvement and the rate of progression vary considerably in Gaucher disease [3-9], but the disease is generally more aggressive in patients who present with symptoms during childhood. Osteopenia, osteonecrosis, osteosclerosis, bone crisis, chronic bone pain, pathological fracture and vertebral collapse can all be associated with Gaucher disease [3,10,11]. Although progression of many of these complications can be halted or reversed by enzyme replacement therapy (ERT), osteonecrosis, osteosclerosis and vertebral compression cannot be reversed. It is therefore imperative that skeletal involvement is assessed early and monitored routinely.

The main goals of imaging bone and bone marrow in Gaucher disease are to estimate the disease burden, to evaluate the presence of specific skeletal complications and to track response to therapy. A variety of techniques have been used including plain radiography, CT, MRI and radionuclide imaging. Newer quantitative technologies and quantitative applications of older technologies are now being tested in Gaucher disease, such as dual-energy X-ray absorptiometry (DXA), quantitative CT and quantitative MRI techniques such as quantitative chemical shift imaging (QCSI) and bone marrow spectroscopy.

We will describe these modalities and their use in imaging and quantifying skeletal complications in Gaucher disease.

QUALITATIVE METHODS

Plain radiography

Plain radiography is almost universally available and is relatively inexpensive, but its sensitivity for defining the pattern of skeletal disease is only 30-40% [12]. Plain radiography is therefore not useful for diagnosing Gaucher disease or monitoring the response of the skeleton to therapy. Instead, plain radiography should be used for detecting complications such as fractures and for monitoring arthroplasty. Arthroplasty failure may be more frequent in patients with Gaucher
disease because of poor bone stock. Plain radiography can also be used to detect modelling disorders such as Erlenmeyer flask deformity of the distal femur and focal lesions such as avascular necrosis. Focal lesions can occur almost anywhere in the skeleton, which necessitates a broad-ranging X-ray screen, which is undesirable, especially in children.

**Computed tomography**

In patients with Gaucher disease, the main use of helical CT is to measure spleen and liver volumes [13,14]. In general, there is no role for CT in assessing bone disease. Applications for CT are generally limited to unusual circumstances, such as when conventional radiographs leave doubt, MRI is unavailable or patients are not MRI-compatible, and sectional images are desired.

**Magnetic resonance imaging**

MRI is the best technique for assessing skeletal involvement in Gaucher disease [15]: It is extremely sensitive to the skeletal pathologies found in Gaucher disease including acute bone infarction, infection, trauma, marrow infiltration with Gaucher cells and avascular necrosis [15-18].

With MRI (T1-weighted spin echo and turbo spin echo sequences, short tau inversion recovery (STIR) sequences, and T2-weighted spin echo, turbo spin echo, or T2* or gradient echo sequences), yellow bone marrow generates a hyperintense signal on T1- and an intermediate to hyperintense signal on T2- and T2*-weighted images in healthy adults (Figure 1A). On STIR sequences, fat marrow appears hypointense. In Gaucher disease, the fat marrow is replaced by the infiltration of Gaucher cells, which dramatically changes the signal to hypointense on T1-, T2- and T2*-weighted images (Figure 1B). In some patients with Gaucher disease, the T1-weighted signal is hypointense and the T2-weighted fat-suppressed or STIR images show hyperintense inclusions (Figure 1C, 1D). This may indicate an active or ‘complicated’ bone marrow process, such as acute bone crisis, occult fracture, infection or bone infarction. In extreme examples, these inclusions appear in over 50% of the femur marrow and are clearly visible on T1- and T2-weighted images (Figure 1E).
Bone marrow changes were evident in the spine of all examined patients with Gaucher disease, even when the involvement of the extremities was variable: this suggests that Gaucher disease is present initially in the lumbar spine, but with progression of disease the extremities become more affected [15]. The Gaucher cell infiltration subsequently extends to
the periphery of the extremities. The epiphysis and apophysis remain relatively unaffected except in the most severe cases. A variety of MRI protocols, all of which include T1-weighted sequences, have been used for imaging bone marrow changes in Gaucher disease [19,20]. A practical approach for MRI of Gaucher bone disease is to evaluate the lumbar spine and/or the lower extremity with conventional T1- and T2- or T2*-weighted spin echo sequences. However, a fat-suppressed sequence, for example STIR or fat-suppressed T2-/T2*-weighted, is mandatory for the detection of complications.

At birth, bone marrow is principally red (40% water, 40% fat, 20% protein) but with maturation the lipid content increases and red bone marrow is converted to yellow bone marrow (15% water, 80% fat, 5% protein), in a centripetal direction, with the epiphysis containing inactive yellow marrow from birth [21,22]. These natural changes in childhood and adolescence can be difficult to distinguish from Gaucher cell infiltration, which consequently makes the assessment of marrow changes in children with Gaucher disease by MRI more difficult. As the conversion from red to yellow marrow has a centripetal spread, the best way to establish severe disease in children may be the imaging of the lower part of the lower extremities, i.e. the tibia and ankle.

**Radionuclide imaging**

Nuclear scans with technetium-99m methylene-diphosphonate (\(^{99m}\text{Tc-MDP}\)) show osteoblastic activity, which could potentially be useful for assessing bone turnover in Gaucher disease. In addition, marrow infiltration and response to therapy in Gaucher disease has been assessed using \(^{99m}\text{Tc-MDP}\), \(^{99m}\text{Tc-sestamibi}\) and technetium-99m hexamethylpropylene amine oxime (\(^{99m}\text{Tc-HMPAO}\)) [23]. These nuclear techniques are very sensitive, but have a lower specificity - the main disadvantage is the poor spatial resolution compared with MRI [8,24]. Radionuclide imaging may help to distinguish between bone crisis and osteomyelitis in Gaucher disease.
**QUANTITATIVE METHODS**

To provide the clinician with a quantitative measurement of bone marrow infiltration, a number of quantitative imaging modalities are being tested in Gaucher disease.

*Quantitative chemical shift imaging*

Quantification of bone marrow changes in patients with Gaucher disease will help to assess disease status and response to therapy. QCSI may be the best method currently available for this.

QCSI, which is a modification of the Dixon technique [25], quantifies the fat content in bone marrow using the differences in the resonant frequencies of fat and water in bone marrow (3.3 ppm). It can therefore detect the reduction in the fat fraction of bone marrow that occurs in Gaucher disease [24,26]. Results obtained with QCSI correlate well with Gaucher disease activity [26] and response to ERT has been detected with this method [27].

Studies using QCSI in Gaucher disease have focused on vertebral bone marrow because abnormalities in vertebral bone marrow are homogenous and located in a fixed region, and because the spine contains active red marrow, which has been shown to change with disease in Gaucher disease and other hematological pathologies [26,28]. Coronal MRI of the lumbar spine is used and the fat content can be represented using a colour scale (Figure 2).

As with all MRI-based quantitative methods, the advantages of QCSI include its non-invasive nature and its ability to measure axial bone marrow. In addition, results with this method are highly reproducible [29]. In 16 healthy adults, the fat content in the lumbar bone marrow was measured twice in the same slice by QCSI and on a third visit the same slice was assessed as well as two parallel slices, 3 mm anterior and 3 mm posterior. The mean fat fraction in this group was 37% and standard deviation of triplicate measurements was only 1.3-3.2%, which could be explained by errors in the slice positioning. In comparison, the marrow fat content measured by QCSI was lower in most of the 31 patients with Gaucher disease tested (Figure 3).
Figure 2. Colour representation of the fat content of lumbar spine measured by QCSI. (A) healthy individual; (B) patient with Gaucher disease with mild bone marrow involvement; and (C) patient with Gaucher disease with severe bone marrow involvement.

Figure 3. Percentage fat content in lumbar spine marrow, measured by QCSI in 31 patients with Gaucher disease before therapy (Academic Medical Center).
Skeletal imaging in Gaucher disease

QCSI shows great promise as a quantitative measure of bone involvement in Gaucher disease. It is now a standard modality at the Academic Medical Center in Amsterdam for assessment of bone marrow burden, and all patients receiving treatment are evaluated annually. The limitations of QCSI are that the technology is not widely available, it does not use a standard MRI sequence (although the sequences are easy to implement) and a dedicated physicist and radiologist are mandatory to gain reliable results.

**Bone marrow H1 spectroscopy**

An experimental quantitative method for detecting relative differences in the fat concentration in bone marrow using H1 spectroscopy has been developed at the Keck School of Medicine of the University of Southern California, USA. The first step in this method is to determine the ratio of fat to water content for both the metaphysis and epiphysis, taking advantage of the 3.3 ppm difference in proton resonant frequencies between fat and water. The ratio of these values is then calculated. This method requires careful placement of the voxel so as to avoid areas of irreversible pathology, which yield unrepresentative fat:water ratios because they contain fluid cavities, fibrous tissue, or calcifications.

In a small study, the metaphyseal/epiphyseal fat:water ratio was significantly lower for patients with Gaucher disease than for normal subjects (0.70 and 1.41, respectively; \( p<0.001 \) [30]. However, until further studies are published the value of this technique for the assessment of clinically relevant bone disease in Gaucher disease is unknown.

**Dual-energy X-ray absorptiometry**

DXA quantifies bone mineral density by measuring the attenuation of the X-ray beam, with correction for soft tissue attenuation. This technique is widely used for assessing bone mineral density in patients with osteoporosis and is also useful for measuring bone mineral density in Gaucher disease [2]. Generalized osteopenia in the patient can be measured by comparing bone mineral densities with healthy age-matched and sex-matched adult controls [2]. The Z scores in patients with Gaucher disease are generally lower than those in healthy individuals, a finding that applies to many parts of the
skeleton (Figure 4) [2]. Furthermore, the severity of osteopenia in patients with Gaucher disease correlates with other indicators of disease severity, such as splenomegaly and hepatomegaly [2]. However, correlation between low bone mineral density and the risk of fractures in post-menopausal osteoporosis [31] cannot be extrapolated to the Gaucher disease population until further research is carried out.

**Figure 4.** Mean bone mineral density at different anatomical sites in patients with Gaucher disease, measured by dual-energy X-ray absorptiometry. Reproduced from *J Bone Miner Res* 1996;11:1801-1807 [2] with permission of the American Society for Bone and Mineral Research.

DXA is insensitive to local changes in bone mineral density, but it is a good measure of generalized osteopenia. As such, DXA may be used to monitor the response of bone mineral density to therapy, although it takes several years of ERT before changes in bone mineral density are detectable [37]. The use of DXA in the patient with Gaucher disease is limited because areas of avascular necrosis, infarction or vertebral body collapse may cause erroneously high bone mineral density readings.
**Quantitative CT**

Dual-energy quantitative CT (DEQCT) is another method for measuring bone mineral density. As with DXA, values obtained using DEQCT are compared with standard values for healthy individuals. Trabecular bone loss may be a better indicator of osteopenia than general bone loss and the biggest advantage of DEQCT compared with DXA is its ability to differentiate between trabecular and cortical bone [24,32,33]. However, DEQCT is not recommended as it exposes the patient to much higher levels of radiation than single-energy quantitative CT (SEQCT) [34]. SEQCT is widely available, is less costly than DEQCT and involves lower radiation exposure than DEQCT. But the use of a single energy makes SEQCT less accurate than DEQCT, because fat marrow influences the measurements.

**Semi-quantitative methods**

**Vertebra-disc ratio**

The clinical utility of the vertebra-disc ratio (VDR), defined as the ratio of the T1-weighted MRI signal intensities of the L3 vertebra and a healthy L3/L4 disc, is being investigated at the Academic Medical Center in Amsterdam [35,36]. Data from 46 healthy adults without bone marrow disorders, degenerative disc disorders, or other pathological conditions of the spinal column showed that the mean VDR was about 1.68, taking into account an age-related increase in VDR. In contrast, the VDR for a patient undergoing radiotherapy, which is associated with an elevated yellow marrow fat content, was 2.6 and the VDRs for two patients with Gaucher disease were 1.00 and 1.23.

**Rosenthal staging system**

A semi-quantitative staging system was developed by Rosenthal et al [15,27], in which 11 sites of Gaucher cell infiltration in the lower extremities are numbered. This is based on the centrifugal spread of disease with infiltration of epiphysis and apophysis in severe disease. The score is the highest numbered site at which MRI demonstrates involvement. This scoring system demonstrated improvement in bone marrow during ERT [27] but was less sensitive than other measures that assess lumbar spine bone marrow. Furthermore, scores using this system are not yet correlated with QCSI results.
Düsseldorf bone marrow disease score

A similar approach has been taken at the Institute of Diagnostic Radiology, Heinrich-Heine-University, Düsseldorf, Germany. Sites of altered marrow (based on MRI) are given a score and the highest numbered site of involvement is taken as a measure of disease severity (Figure 5). In 63 patients with Gaucher disease, an abnormal low MRI signal intensity was observed in areas 1 and 2 of the femur in 98% of patients, in area 3 of the femur in 88%, in areas 4 and 5 of the tibia in 74%, in areas 6 and 7 (the epiphyses of the knees) in 39%, and in area 8 of the tibia in 36% [20]. This finding confirms previous studies showing that the epiphyses of the knees are spared in most patients with Gaucher disease. This scoring system suffers the same problems with sensitivity as the Rosenthal system, but did correlate with other symptoms of severe disease. The score in 13 patients with femoral head necrosis was 7.8 whereas in 49 patients without femoral head necrosis the score was 5.6 ($p < 0.0001$; unpublished results).

Figure 5. The Düsseldorf Gaucher score (modified "Rosenthal-score" [15]); anatomical score of the lower extremities for quantification and localization of bone marrow abnormalities.

Bone marrow burden score

At the Academic Medical Center in Amsterdam, a bone marrow burden scoring system has been developed that takes into account the progressive pattern of infiltration in the lumbar spine and the femur. Its use in the assessment of treatment response compared with QCSI is being evaluated in ongoing studies.
**Classification and indirect measures**

At the Keck School of Medicine, a system of classifying the severity of bone marrow infiltration in patients with Gaucher disease has been developed based on the changes in MRI signal intensities shown in Figure 1 (Table 1). Bone marrow involvement is further subclassified based on the absence or presence of avascular necrosis. One finding at the Keck School of Medicine was that avascular necrosis was much more prevalent in classes 2 and 3 than in classes 0 and 1, suggesting that this system of classification may have some prognostic value.

**Table 1.** Bone marrow classification based on T1- and T2-weighted signal intensity and avascular necrosis

<table>
<thead>
<tr>
<th>Class</th>
<th>T1-weighted signal</th>
<th>T2-weighted signal</th>
<th>Avascular necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0a</td>
<td>normal</td>
<td>normal</td>
<td>absent</td>
</tr>
<tr>
<td>0b</td>
<td>normal</td>
<td>normal</td>
<td>present</td>
</tr>
<tr>
<td>1a</td>
<td>decreased</td>
<td>decreased</td>
<td>absent</td>
</tr>
<tr>
<td>1b</td>
<td>decreased</td>
<td>decreased</td>
<td>present</td>
</tr>
<tr>
<td>2a</td>
<td>decreased</td>
<td>increased</td>
<td>absent</td>
</tr>
<tr>
<td>2b</td>
<td>decreased</td>
<td>increased</td>
<td>present</td>
</tr>
<tr>
<td>3a</td>
<td>decreased</td>
<td>increased &gt;50%, heterogenous</td>
<td>absent</td>
</tr>
<tr>
<td>3b</td>
<td>decreased</td>
<td>increased &gt;50%, heterogenous</td>
<td>present</td>
</tr>
</tbody>
</table>

Preliminary data from the Keck School of Medicine suggest that the degree of visceral response to ERT may be correlated with the response of bone marrow. In 14 patients who responded to ERT, there was a significant correlation between a bone marrow response (from the T1-weighted image) and the reduction in the volume of the liver ($p<0.005$) or spleen ($p<0.005$) [19].

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Another Gaucher disease bone marrow classification system based on the pattern of T1- and T2-weighted images has been used at the Institute of Diagnostic Radiology, Düsseldorf [20]. In this system, a homogenous pattern of bone marrow is classified as type A morphology and a heterogenous or patchy pattern is classified as type B morphology (Figure 6). The rationale behind this classification was the assumption that a heterogenous pattern of bone marrow signal intensity represents a higher incidence of irreversible bone changes. In 63 adults with non-neuronopathic Gaucher disease, type B bone marrow morphology correlated with more severe skeletal disease ($p<0.0001$) and the presence of bone infarcts ($p=0.0021$).

**Figure 6.** Coronal T1-weighted spin echo images of the lower extremities showing morphology type A [6A and 6B] and B [6C and 6D].
**DISCUSSION**

The skeletal complications of Gaucher disease are generally progressive but have an unpredictable course, and the response to therapy must be monitored in order to make decisions regarding dosage. The use of radiological imaging for patients with Gaucher disease should therefore not be restricted to differential diagnosis of skeletal complications, but should be performed at regular intervals.

Although the choice of radiological imaging techniques used to examine these patients is influenced by practical considerations such as availability and cost, this discussion will concentrate on the applicability of the technique to Gaucher disease.

MRI is the most widely applicable imaging technique for the skeletal complications of Gaucher disease, as it can used to detect infarction, infection, focal lesions, fractures, red marrow expansion, and bone marrow infiltration. This method is widely available in many western countries. It is the best technique for evaluating bone marrow infiltration in Gaucher disease. The main disadvantage of conventional MRI for evaluating bone marrow is that it is not quantitative.

Several MRI-based quantitative methods for measuring bone marrow infiltration in patients with Gaucher disease are being investigated, including Dixon QCSI, T1-relaxation calculations, and NMR spectroscopy. Dixon QCSI may become the standard quantitative method but protocols for this technique are not yet standardized. Furthermore, it is only available at a few centres worldwide. The majority of Gaucher patients therefore cannot currently benefit from this technique. Semi-quantitative scoring systems based on MRI and indirect methods for assessing bone marrow infiltration are also being researched. The advantage of the MRI scoring systems is that they are no more difficult or expensive than MRI and could become as widely available as conventional MRI, but the clinical relevance of these techniques for monitoring response to ERT is unknown. The ideal quantitative method for measuring skeletal complications and response to ERT in patients with Gaucher disease would be easy to perform, inexpensive, widely available, non-invasive, and the results would be consistent with skeletal outcome data. At present, no method for measuring skeletal involvement in Gaucher disease meets all these criteria.
A consensus on the optimum site of measurement must be reached before any quantitative or semi-quantitative technique for measuring bone marrow infiltration becomes widely accepted. Evaluation of the bone marrow of the lumbar vertebra and femur both have clinical advantages and disadvantages. In addition, a better understanding of the pathophysiology of changes in bone marrow morphology on MRI. For example, if a region that previously showed a homogenous signal of normal intensity on T2*-images later shows a heterogenous pattern, this may indicate an active disease state that may be irreversible. However, if a region of homogenous hypointense signal intensity on T1- and T2-weighted images shows a heterogenous pattern after ERT, this could indicate areas of bone marrow responding to treatment adjacent to areas of irreversible change.

A number of disease staging systems have been developed. These systems are less sensitive than QCSI for detecting response to ERT, and the absence of a standardized system may reflect our limited understanding of the natural history of Gaucher disease.

Plain radiography may be used for imaging orthopedic complications such as fractures and arthroplasty failure and for detecting focal lesions such as avascular necrosis. This technique has the advantages of being widely available and inexpensive. However, because of the low sensitivity of plain radiography, lesions initially detected with plain radiography may not show a response to therapy on follow-up plain radiography investigations. Plain radiography should therefore not play a major role in tracking or monitoring the skeletal response to therapy in Gaucher disease.

DXA and quantitative CT can provide quantitative data for assessing generalized osteopenia and measuring bone mineral density. Measurements with both of these techniques are compared with those of healthy, age- and sex-matched subjects. DXA may be used to measure response to ERT but quantitative CT currently plays a more scientific than practical role. In the absence of collapsed vertebrae, the lumbar spine may be the best site to use when measuring changes in bone mineral density with therapy, and the same site should be used during each assessment. More research is required to determine the long-term value of bone mineral density measurements in patients with Gaucher disease, for example to investigate the relationship between bone mineral density and fracture risk in these patients.
Skeletal imaging in Gaucher disease

In conclusion, MRI is the most appropriate technique for assessing many of the skeletal manifestations, particularly bone marrow complications, of Gaucher disease. DXA is the most useful method for measuring bone mineral density. More research is needed to develop and optimize quantitative methods for measuring bone marrow infiltration and to understand the pathophysiology of skeletal complications of Gaucher disease so that the risk of complications may be predicted and the response to ERT optimized.

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REFERENCES
Chapter 3


