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

Citation for published version (APA):
Ridderkerk: M. Maas

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The vertebra-disc ratio as a parameter for bone marrow involvement and its application in Gaucher disease

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ABSTRACT

Objective:
To establish the Vertebra Disc Ratio (VDR), the ratio of the average T1-weighted gray value of vertebral body L3 and intervertebral disc L3/L4, as a parameter for bone marrow involvement. To explore its value as alternative for bone marrow fat fraction (Fp) measured with Dixon quantitative chemical shift imaging (Dixon QCSI) in Gaucher disease.

Methods:
Age dependency and normal value for the VDR were determined in 46 controls. The VDR in untreated Gaucher disease (N=22) and long treated Gaucher disease (7.5 years, N=19) were compared to the controls. VDR as follow-up parameter was tested in treated Gaucher disease patients (N=33) and untreated Gaucher disease patients (N=8). The correlation between VDR and Fp was determined.

Results:
Age dependency was small. The normal VDR was 1.90 ± 0.30. Both untreated Gaucher disease (1.29 ± 0.31) and long treated Gaucher disease (1.70 ± 0.33) differed significantly from normal. Changes in treated Gaucher disease were significant in the first four treatment-years, in untreated Gaucher disease patients no significant changes were observed. The correlation with Fp was 0.86.

Conclusions:
The VDR is a useful parameter for evaluation of bone marrow of patients with Gaucher disease. The VDR correlates very well with Fp, so applicability is expected in diseases in which Fp has proven to be useful.
INTRODUCTION

In the radiological follow-up of infiltrating bone marrow diseases, the bone marrow fat-fraction plays an important role, as it has been shown that this quantity correlates well with disease-activity [1]. The fat-fraction can be measured using Dixon quantitative chemical shift imaging (Dixon QCSI), or with proton MR spectroscopy [2-9]. Dixon QCSI allows for the measurement of the axial bone marrow, and has good reproducibility [10]. To our best knowledge the use of Proton MR Spectroscopy to measure fat-fractions in a routine clinical setting has not been investigated.

Gaucher disease, the most prevalent lysosomal storage disorder, is caused by a deficiency of the enzyme glucocerebrosidase leading to accumulation of glycolipids in macrophages (Gaucher cells) [11]. These cells accumulate in the liver, spleen, and bone marrow. The most important clinical consequences are hepato-splenomegaly, pancytopenia, skeletal disease, and bone marrow infiltration [1,3,10-14]. Measurement of the Gaucher cell burden in the axial skeleton in untreated patients might be used as a prognostic tool for bone complications, and may indicate the need to start therapy. Since enzyme supplementation therapy for Gaucher disease [15-17] is very expensive, monitoring therapy-response is mandatory to optimize individual dosage scheme [17]. Dixon QCSI measured fat-fraction ($F_f$) has been advocated as the best suitable tool for this purpose [18].

Although $F_f$ is considered the state-of-the-art modality to monitor bone marrow infiltration, a problem with this technique is that it is not widely available; special non standard MR sequences are needed, as are special post-processing tools [19,20]. In the following we propose an alternative for the bone marrow fat-fraction that is widely available and easy to use.

On plain T1-weighted images, the bone marrow of untreated patients with Gaucher disease shows a decrease in signal, because normal bone marrow fat is replaced by Gaucher cells [1] which has a low signal intensity. This reduced T1-weighted signal, however, cannot be used directly for bone marrow evaluation, since it depends on different amplification factors some of which are unknown. The inclusion of an internal reference signal leading to a ratio between these two values may solve this problem. We defined the Vertebra Disc Ratio (VDR) as the T1-weighted bone marrow signal divided by the signal of the healthy adjacent intervertebral disc, and investigated whether this could be a
valid alternative to $F_r$. This was done by measuring the normal range for the VDR, comparing this to the VDR in Gaucher disease, investigating whether the VDR is able to detect changes in response to therapy and calculating the correlation between the VDR and $F_r$.

**METHODS AND MATERIALS**

*Patients and Controls*

This investigation was carried out at a University Hospital, which serves as a national referral center for Gaucher disease [17]. Patients with Gaucher disease visited the hospital roughly every year between 1993 and 2001. Patients were retrospectively included if 1) sagittal T1- and T2-weighted images of the lumbar spine were available, 2) vertebral body L3 was intact, and 3) intervertebral disc L3/L4 was intact. Exclusion criteria were: other bone marrow disorders, malignancies, radiotherapy, recent bleeding, liver disease and renal impairment [21]. The $F_r$ of the same patient was included in this study if the image acquisition was performed within one day of the acquisition of the T1-weighted images. We also registered whether or not a patient was under therapy.

As controls served patients undergoing MR imaging of the lumbar spine in whom no abnormalities in the vertebrae or intervertebral discs were found. Control patients were retrospectively included under the same inclusion and exclusion criteria as the Gaucher disease patients.

*Data Acquisition and Processing*

All conventional MR imaging was done on a 1.5T magnet (Vision, Siemens, Erlangen, Germany), using a dedicated spine coil. Routine sagittal T1-weighted and T2-weighted spin echo images were acquired. For T1-weighted imaging TE and TR ranged from 12-15 ms and 400-650 ms respectively. The VDR was calculated from the vertebral body L3 in the mid-sagittal T1-weighted spin echo image of the lumbar spine, and the intervertebral disc L3-L4 in the same image.

To exclude cortex from the measurement and to avoid partial volume averaging the edge of the above mentioned structures was excluded as follows: both vertebral body L3 and intervertebral disc L3/L4 were outlined manually using an image processing program (Photoshop 5.0, Adobe, San Jose, California, USA), see figure 1 [22]. The Regions of Interest (ROIs) thus obtained, were downsized towards the center by
15-25% using erosion, which is a morphological image processing procedure [23]. From these smaller, central ROIs the VDR was calculated as the ratio of their average gray-values.

For Dixon QCSI imaging, in-phase and opposed-phase proton density weighted spin echo sequences were performed with a TR of 2500 ms and a TE of 22.3 ms [19]. The measurement acquisition slices were positioned coronally. Post-processing and data analysis were performed using a previously described algorithm [20]. To obtain one fat-fraction value for L3, the pixel values were averaged over a user-defined ROI. This ROI was achieved in a similar way as described above, by outlining the cortex of L3 and then reducing the ROI’s size.

**Statistical analysis**

All statistical analyses were performed on a Pentium PC, using Microcal Origin v. 6.0, Northampton, Massachusetts, USA. Differences between groups and differences from zero were tested with Student’s t-test. Response of VDR under therapy was assessed by comparing values from two adjacent years. To establish relations between quantities (e.g., VDR vs. age, VDR vs. F) we applied linear fitting (a linear fit is a way to calculate an assumed linear relationship between two quantities) and correlation coefficients where appropriate.

**Figure 1.** These images are from a Gaucher disease patient receiving treatment. The left is from 1997, the right from 2000. The VDR’s were 1.20 and 1.95 respectively. In the right image the contours that were used for calculation of the VDR are shown.
Statistical significance was obtained when \( p<0.05 \) or (equivalently) when 95% confidence interval (CI) did not overlap.

**RESULTS**

*Patients and Controls*

46 Gaucher disease patients were included (26 females, age range 19 - 71, average 42.8 years), (20 males, age range 26 - 61, average 42.2 years). 24 Patients were receiving therapy at inclusion, 13 patients started therapy during this investigation and 9 patients remained untreated.

The average number of VDR measurements per patient was 4.4, ranging from 1 to 7. These measurements spanned an average of 4.3 years, ranging from 0 (only one measurement done) to 7 years. The total number of VDR measurements was 204, the total number of simultaneously measured \( F_f \)'s was 126.

46 Control patients were included, 20 males (age range 6.2 - 71.4) and 26 females (age range 2.8-71.3), with an average age of 39.9. A subgroup of 33 control patients was selected which age-matched the Gaucher disease patient group: the average age of the subgroup was 40.7, range 25.5-60.0.

*VDR in controls*

The average VDR of all controls (N=46) was 1.90 (standard deviation (SD) 0.30, standard error of the mean (SEM) 0.04). The average VDR of the age-matched subgroup (N=33) also was 1.90 (SD 0.30, SEM 0.05).

As the VDR is meant to serve as a longitudinal bone marrow follow-up tool and fat-fraction may increase with age [21,22], it was important to establish whether or not an age dependency existed. We assumed the following linear relationship between the VDR and the AGE of all control patients (N=46):

\[
\text{VDR} = a + b \times \text{AGE (years)}
\]

and the fitting procedure found the following optimal result for \( a \) (the intercept) and \( b \) (the slope, which reflects the actual age dependency), with the 95% CI in brackets:

\[
a = 1.63 \ (1.52, 1.73)
\]
\[
b = 0.007 \ (0.002, 0.011)
\]

The fit is visualized in figure 2.

Since the 95% CI for the slope does not include zero, the age dependency is significant. It is, however, small: 0.007 increase in VDR per year.
Comparing this to the group standard deviation (SD 0.30, SEM 0.053) and to the changes due to therapy (0.14 in the first year, see below), we found it justified to neglect the age dependency in the further analyses, even more so since we used an age matched subgroup.

**Figure 2.** The linear fit (dashed line) between Vertebra Disc Ratio and Age for the controls (N=46).

*VDR in Gaucher disease patients*

From all the available VDR-measurements at which the patient was not receiving therapy the most recent one was selected to get one measurement per patient (N=22, average age 40.2 years, range 28.8 - 59.3 years). The average VDR in this group was 1.29 (SD 0.31, SEM 0.066). This is significantly lower ($p < 10^{-8}$) than the VDR values of the control patient group.

The date at which therapy started was defined as $T=0$ for each patient individually. The changes in VDR during therapy were calculated per year, using only measurements that had a time interval of 0.9 to 1.1 year. For 33 patients we had at least 2 such measurements. The yearly changes are given in Table 1, showing a significant average increase in VDR during the first four years of treatment of 0.10 to 0.14. From the fifth to the seventh year of treatment we see no significant change.

The untreated Gaucher disease-patients (N=9) did not visit as regularly as the treated patients and for these patients the method used to calculate changes in VDR, as described above, could not be used.
### Table 1

Average yearly changes in Vertebra Disc Ratio (VDR) for patients receiving therapy. The change reported is the change that happened the year before, e.g. year 1 reports the change that occurred between start of therapy and one year after. The change in VDR is given with the 95% confidence interval in brackets. The change is statistically tested against the normal age related change; $p$-values marked with an asterisk are considered significant ($p<0.05$).

<table>
<thead>
<tr>
<th>Treatment Duration</th>
<th>N</th>
<th>Change in VDR</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>11</td>
<td>0.14 (0.07, 0.22)</td>
<td>*0.005</td>
</tr>
<tr>
<td>2 years</td>
<td>12</td>
<td>0.10 (0.04, 0.17)</td>
<td>*0.01</td>
</tr>
<tr>
<td>3 years</td>
<td>11</td>
<td>0.12 (0.02, 0.21)</td>
<td>*0.04</td>
</tr>
<tr>
<td>4 years</td>
<td>13</td>
<td>0.14 (0.05, 0.23)</td>
<td>*0.01</td>
</tr>
<tr>
<td>5 years</td>
<td>12</td>
<td>0.09 (-0.01, 0.18)</td>
<td>0.13</td>
</tr>
<tr>
<td>6 years</td>
<td>7</td>
<td>-0.04 (-0.18, 0.11)</td>
<td>0.57</td>
</tr>
<tr>
<td>7 years</td>
<td>6</td>
<td>0.07 (-0.04, 0.18)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

For eight untreated patients we had more than one measurement, and we took the difference of the first and last available measurement, divided by the time (in years) between the two measurements, to estimate the average change per year. The average time between the first and last measurement was 2.6 years, ranging from 1 to 4 years. The resulting mean change in VDR per year was 0.03, with a 95% CI of (-0.08, 0.16). This is in agreement with the age dependency found in the controls. The average VDR in treated Gaucher disease was calculated from measurements at which a Gaucher disease patient had received an average of 7.5 years of treatment (range 6-9 years); data were available for 19 individuals. The average VDR was 1.70 (SD 0.33, SEM 0.076). While this is still significantly ($p=0.032$) lower than the VDR values of the control group (1.90), it is also significantly higher ($p=0.0002$) than the VDR in untreated Gaucher disease (1.29).


VDR and Gaucher disease

**VDR versus Dixon QCSI fat-fraction**

A total of 126 simultaneously measured VDRs and \( F_f \)'s were available. Assuming the following linear relationship between \( F_f \) and VDR:

\[
F_f = c + d \times VDR
\]

the fitting algorithm found optimal values for the intercept \( c = -0.18 \) (-0.24, -0.13) and for the slope \( d = 0.32 \) (0.28, 0.35) with 95% CI in brackets, both being significantly different from zero. This is visualized in figure 3. The correlation coefficient \( R = 0.86 \) (0.72, 1.00) also was highly significantly different from zero \((p < 0.0001)\).

As it was uncertain whether the relation between VDR and \( F_f \) was the same for treated and untreated patients, the fit and the correlation were repeated also for two subgroups: 1) for untreated Gaucher disease patients (1 value per patient) and for 2) treated Gaucher disease patients (2 - 4 years of treatment, preferably around 3 years of treatment, 1 value per patient).

Complete results are given in table 2. The fitting coefficients do not differ significantly between the three sets of data, which can be told from the (partly) overlapping 95% confidence intervals.
Table 2. Fit and correlation results for Vertebra Disc Ratio (VDR) and Fat-fractio n ($F_f$). The formula of the fit is $F_f = c + d \times VDR$. Coefficients c and d and the correlation R are given with their 95% confidence intervals. Results are given for patients receiving no therapy, patients having received two to four years of therapy, and all available simultaneously measured VDRs and $F_f$'s (with multiple values per patient).

<table>
<thead>
<tr>
<th>Therapy</th>
<th>N</th>
<th>c</th>
<th>d</th>
<th>Correlation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>19</td>
<td>-0.08</td>
<td>0.24</td>
<td>0.77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-0.21, 0.06)</td>
<td>(0.15, 0.34)</td>
<td>(0.64, 0.91)</td>
<td></td>
</tr>
<tr>
<td>2 to 4 years</td>
<td>17</td>
<td>-0.15</td>
<td>0.30</td>
<td>0.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-0.31, 0.01)</td>
<td>(0.20, 0.39)</td>
<td>(0.69, 1.00)</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>126</td>
<td>-0.18</td>
<td>0.32</td>
<td>0.86</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-0.24, -0.13)</td>
<td>(0.28, 0.35)</td>
<td>(0.72, 1.00)</td>
<td></td>
</tr>
</tbody>
</table>

**DISCUSSION**

Bone marrow infiltration is a serious clinical problem in Gaucher disease. To quantify this infiltration, the fat-fraction measured with Dixon quantitative chemical shift imaging ($F_f$) is state-of-the-art. However, an alternative is needed in those places where patients with Gaucher disease are treated, but $F_f$ is not available. In this article it has been investigated whether or not the VDR is a valid alternative.

A normal range for the VDR has been established. The VDR is age dependent, though the age-dependency is very small; therefore it was ignored for the evaluation of bone marrow in Gaucher disease.

The VDR differs significantly between healthy bone marrow (controls) and bone marrow from untreated patients with Gaucher disease. The yearly VDR-changes are significant during the first four years in treated Gaucher disease patients. Although the average VDR in Gaucher disease patients is still below normal after an average therapy duration of 7.5 years, it is much higher than the average VDR in untreated Gaucher disease patients. Even though no yearly changes are significant after 4 years of treatment, this does not imply that no change occurs; it is more likely that the changes are too small to be detected with the given group.
size. We will have to wait and see whether the average VDR in Gaucher disease returns to normal after an even longer therapy duration. The VDR correlates very well with \( F_p \). This correlation is the same in treated and untreated Gaucher disease.

**Limitations**

The normal value of the VDR has been calculated from a transverse cohort. Therefore, it is unknown what the normal longitudinal variation is. However, the use of the VDR is intended to be longitudinal. Its use in clinical practice will have to learn what normal longitudinal variations are.

The controls that were referred for MR imaging of the lumbar spine cannot be considered a healthy population, since MR of the lumbar spine was requested. The "true" normal VDR might deviate from the one published here.

In this article, the VDR has been compared to \( F_p \). The VDR was subject to some factors which potentially increased its variance: For \( F_p \) the imaging plane from which the data was calculated was chosen coronal to be as much parallel as possible to the coil, to reduce the effects of signal drop off caused by the surface coil. The data for the VDR were calculated from sagittal planes. TE and TR were fixed for \( F_p \) for the VDR they varied. The \( F_p \) was calculated from the bone marrow alone; the VDR included the intervertebral disc. It is known that the water content of the disc is influenced by age [24] and can even vary within a day [25,26]. This influences the VDR, giving rise to non bone marrow related changes.

In spite of these factors the VDR shows a very good correlation with \( F_p \), independent of the treatment status of the patient.

**Conclusions**

We conclude that the VDR is a very useful parameter for the radiological follow-up of bone marrow of patients with Gaucher disease. Group effects can be measured directly, for individual follow-up one has to bear in mind that the variations over time have not been measured in healthy controls.

With the VDR, a tool has been made available that allows any center with a 1.5 T MR scanner to do reliable bone marrow measurements in patients with Gaucher disease; previously this was limited to centers being able to perform Dixon QCSI. This tool opens new doors for research: if images
have been stored digitally, retrospective studies on Gaucher disease patients are possible, as most lumbar spine imaging includes T1-weighted images. It is also allowed for comparisons between different centers. Even though different centers will have different choices for TE and TR in T1-weighted images, this should not pose a problem as the VDR has not been defined with a very strict TE or TR.

For individual patient follow-up the VDR can be used as another parameter for monitoring therapy-response.

**Future applications**

As the correlation between $F_f$ and VDR was very good, and independent of the treatment-status of the patient, we expect applicability in other diffuse bone marrow diseases in which $F_f$ has proven to be useful. These include leukemia [5,27,28], aplastic anemia [5], malignant lymphoma [29], and myelofibrosis [29]. Also, the follow-up of autologous blood stem cell transplantation [30] is possible.

As proton MR spectroscopy and $F_f$ both can be used to measure bone marrow fat-fractions, we also expect a potential use for the VDR in areas where fat-fractions measured with proton MR spectroscopy have proven their value: bone weakness and osteopenia [31,32], aplastic anemia [33], the effects of chemotherapy [34], and even bone marrow changes in anorexia nervosa [35].

**References**


