

Quantitative NMR imaging in Pompe patients to monitor the progression of skeletal muscle alterations without and with enzyme substitution therapy

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TARGET AUDIENCE: Researchers and clinicians with interest in neuromuscular diseases and biomarkers for therapeutic trials.

PURPOSE. The adult form of type II glycogenosis (GSDII) is a slowly progressive disease, with a few notable exceptions of patients who remain remarkably stable during decades and others who quite suddenly start to degrade very quickly. A number of GSDII patients with non-typical presentation are mis-diagnosed or diagnosed late. Whole-body muscle NMR imaging has proven useful to identify yet unrecognized GSDII patients, with the detection of muscle fatty infiltration patterns that are highly suggestive of the disease (1).

Quantitative NMR imaging has interesting diagnostic applications but its primary role is to provide non-invasive biomarkers and assess disease progression and/or response to intervention. Studies have reported the effect of enzyme substitution therapy on muscle mass shown using NMRI (2, 3). Imaging biomarkers may be of particular importance for adult-form GSDII therapeutic trials, where clear demonstration of a clinical benefit has been difficult to document. Muscle water T2 increase is a non-specific process but it closely relates to “disease activity”, whatever the underlying mechanisms are: inflammation, necrosis, oedema. In FSHD patients, it has been suggested that abnormal T2 is predictive of fatty degenerative changes development in subsequent years (4).

In this study, we analyzed the imaging data collected on the cohort of adult GSDII patients followed at the Institute of Myology. We focused our attention on **the possible link between an elevated muscle water T2 and the progression of fatty infiltration between yearly scans.**

SUBJECTS AND METHODS. NMR imaging was performed on a 3T Magnetom Trio TIM scanner (Siemens Erlangen) operating with arrays of surface receiver coils. Muscle imaging was part of the routine yearly follow-up of GSDII patients at the Institute of Myology. The following sequences were acquired:

- Lower limb axial T1w SE
- Lower limb fat-water 3point 3D Dixon proton density GE
- 2 stacks of multi TE SE centered on the thighs and legs
- 3D AFI B1 mapping at the same levels as the multi TE SE

T2 maps were generated using the multi-exponential fitting and B1-based voxel sorting developed in our laboratory (5).

23 patients underwent a total of 59 scans, all but 8 involving both legs and thighs. Enzyme substitution therapy was administered to 14 patients. Direct comparison between treated and untreated patients was impossible because decision to treat was based on the severity of the disease, as assessed clinically. This did not prevent to study the impact of treatment on the muscle structural changes over time.

RESULTS. Despite the slow course of the disease in adults, a high percentage of muscles were found with an abnormally high water T2 : **32% of muscles had a water T2 above 39ms** (see fig. 2). No correlation was observed between T2 and muscle fat content.

The progression of fatty degenerative changes as estimated by the fat fraction derived from Dixon acquisitions was remarkably slow : **0.9±0.2%/yr.**

Despite this very low average figure, the independent impact of an elevated muscle water T2 and of an enzyme substitution therapy on muscle fatty degenerative changes were evidenced (see figure 3).

Muscles with an elevated T2 experienced a fatty infiltration progression accelerated on average by 0.61%/yr (p=0.02). Enzyme therapy slowed down the fatty degenerative changes on average by 0.68%/yr (p=0.01).

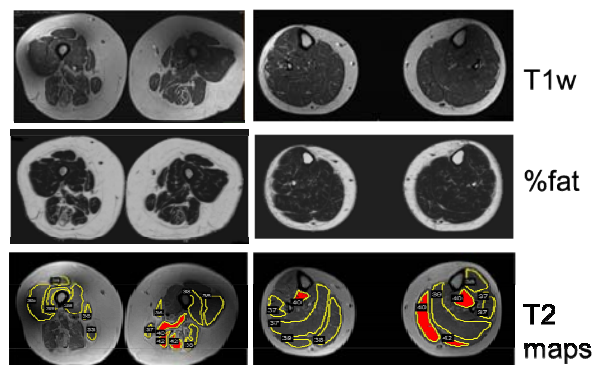


Fig. 1. Example of lower limb imaging in a GSDII patient. Upper panel shows routine T1w SE. The %fat are parametric images calculated from Dixon water-fat imaging acquisitions. The T2 maps quantify the degree of disease activity in muscles. Abnormal T2s are displayed in red.

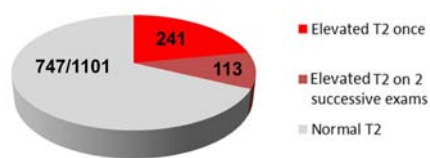


Fig. 2. Statistics of muscle T2s when determined twice at one year interval. About one third of all leg and thigh muscles had abnormal T2 on at least one occasion.

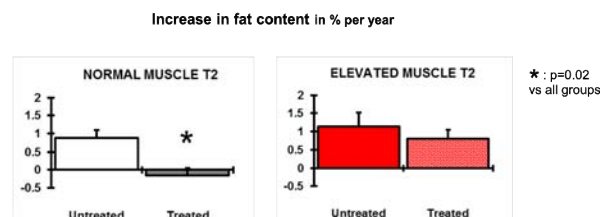


Fig. 3. Muscles with an abnormal T2 experienced a faster progression of the fatty degenerative changes. The enzyme substitution therapy was able to slow down the progression of the muscle fatty degeneration. While highly significant from a statistical perspective, these changes were of small amplitude, typically less than 1%/year.

DISCUSSION AND CONCLUSION.

- Up to a third of muscles of GSDII patients have abnormal T2 values, reflecting disease activity
- Progression of the fatty degenerative changes is on average less than 1% per year
- Fatty degenerative changes progression is aggravated in high T2 muscles
- Fatty degenerative changes progression is slowed down by enzyme therapy
- These figures will make the demonstration of newer therapeutic approaches superiority extremely challenging, particularly in multi-center trials

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