MRI/MRS assessment of the status of skeletal muscle in DMD patients

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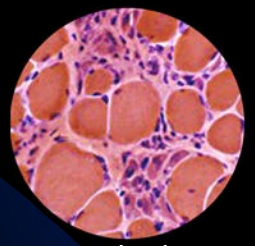
Natural History

	Controls	DMD
Number	36	136
Mean Age (years)	9.7 (±2.3)	8.3 (±2.2)
Steroid positive (number)	NA	100
BMI	17.3 (±3.5)	18.8 (±4.1)

- **CHOP** - Philadelphia, PA
- **OHSU/Shriner's** – Portland, OR
- **UF -** Gainesville, FL

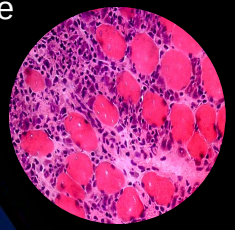
- Krista Vandenborne (UF), Director
- Lee Sweeney (UPenn/CHOP), Co-Director

Magnetic Resonance Biomarker

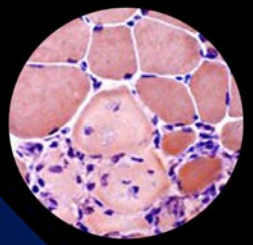


Muscle damage

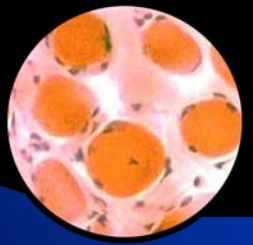
MR Targets



Inflammation



Atrophy and Hypertrophy



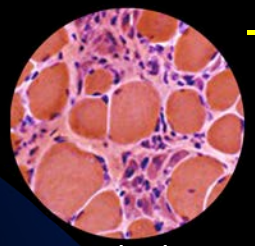
Fiber replacement

Secondary processes

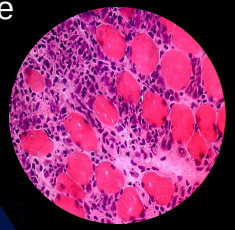
Disease Progression

Magnetic Resonance Biomarker

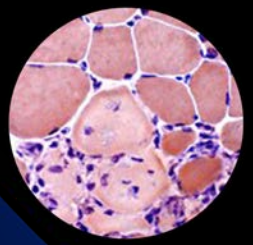
Most useful MR parameters:
- Fat fraction (% of muscle replace by fat)
- Quantitative T_2 imaging



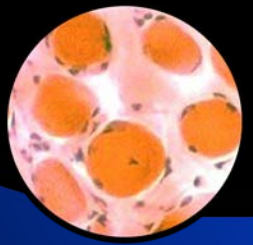
Muscle damage



Inflammation



Atrophy and Hypertrophy



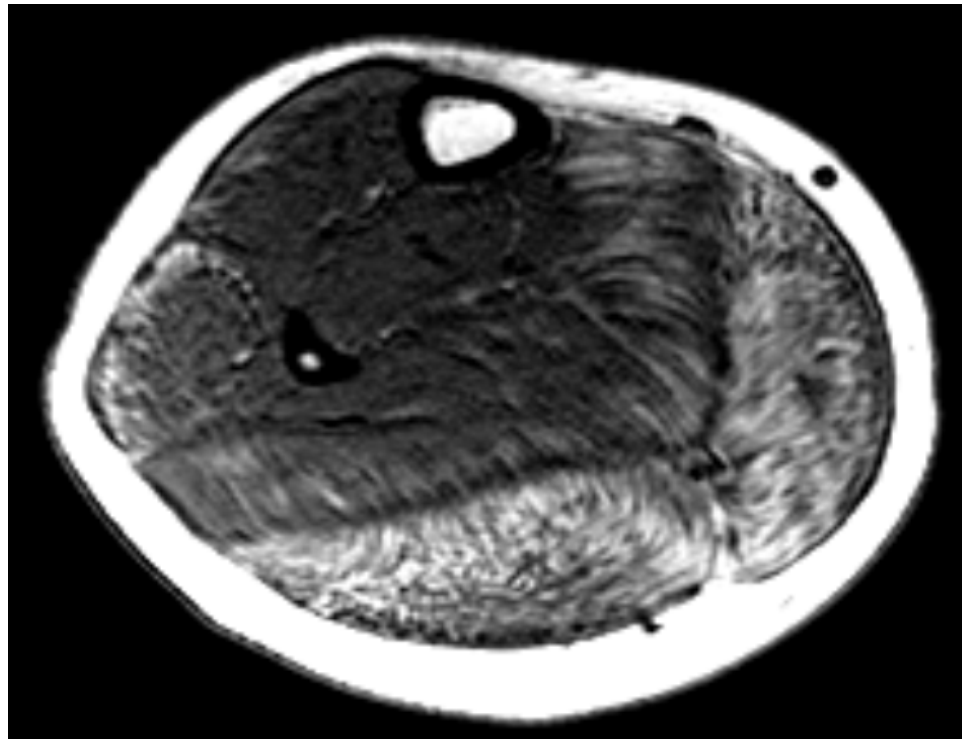
Fiber replacement

Secondary processes

Disease Progression

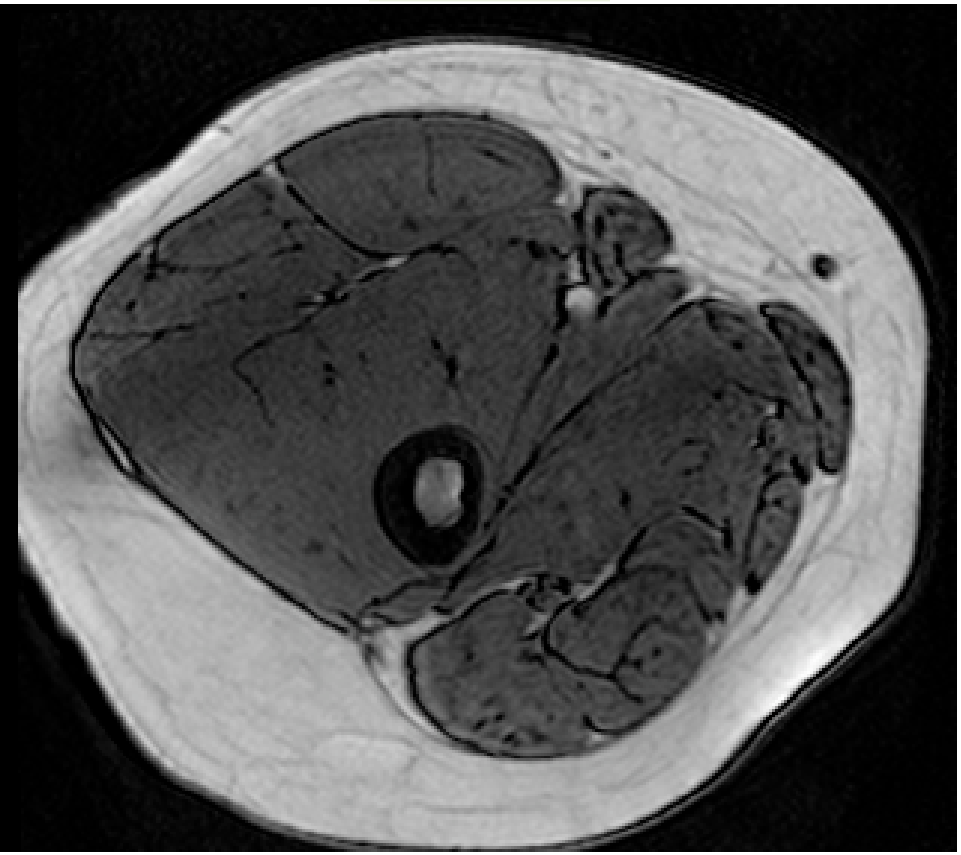
Control

Duchenne

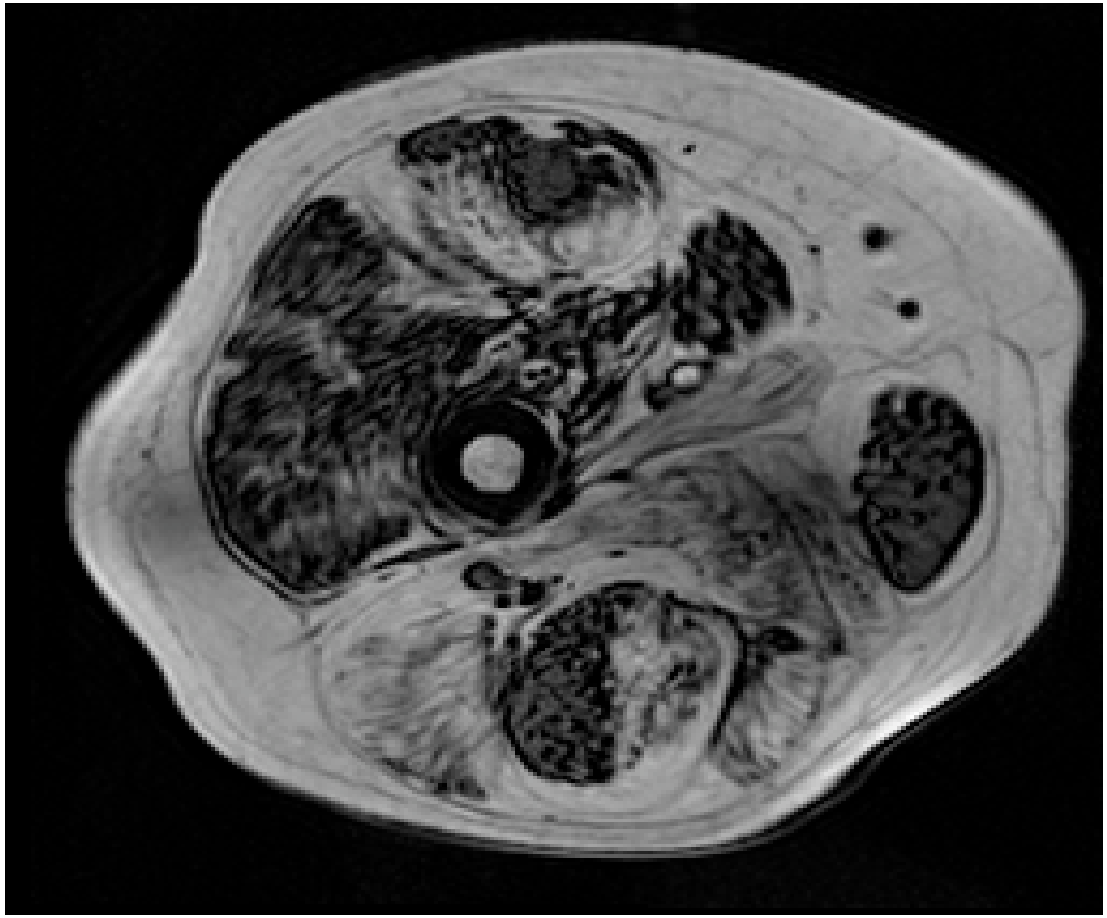


Lower leg muscles

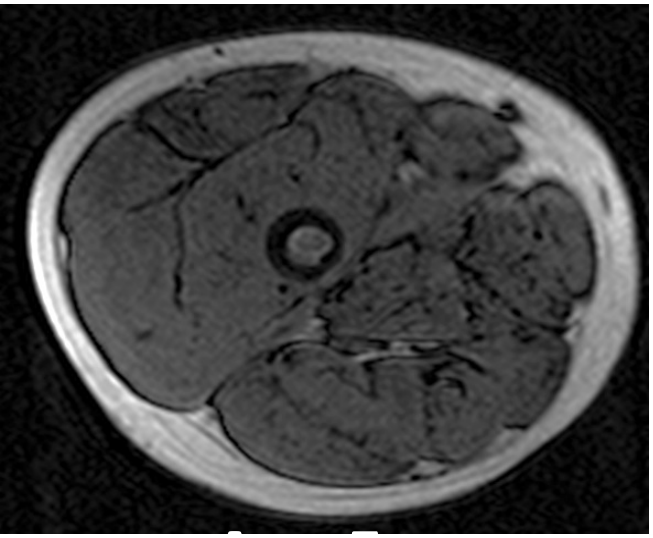
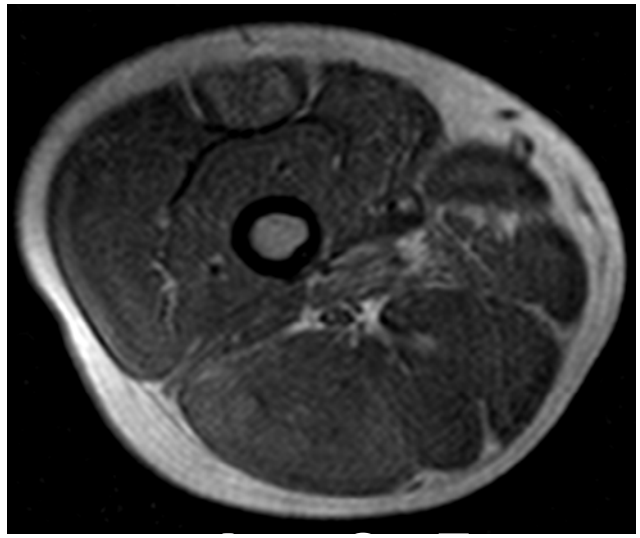
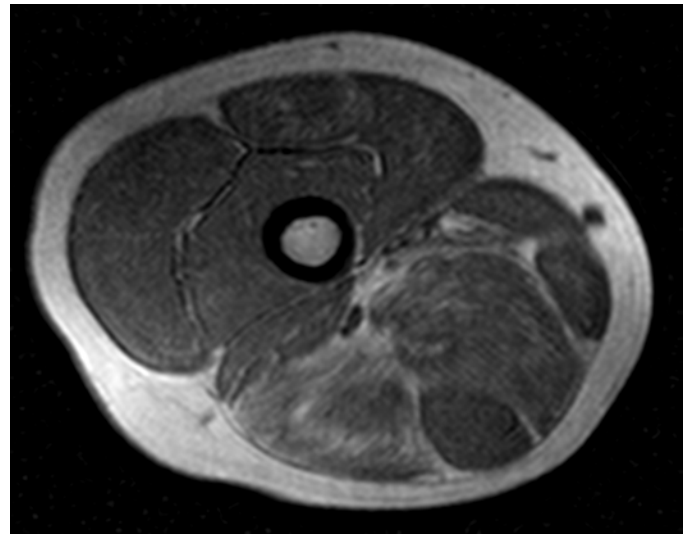
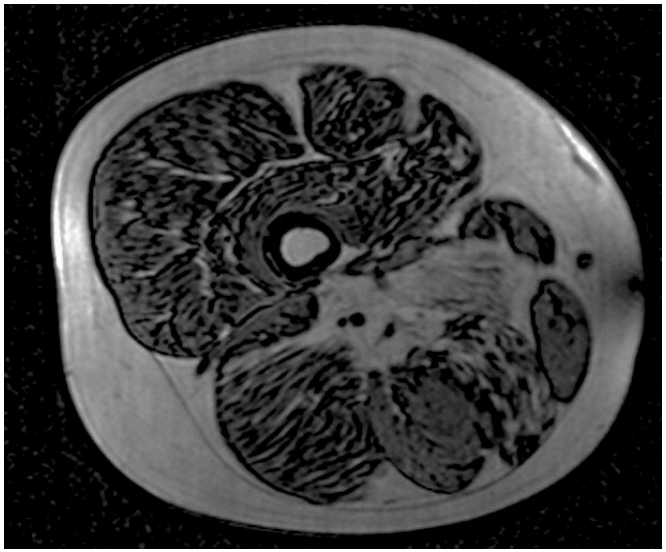
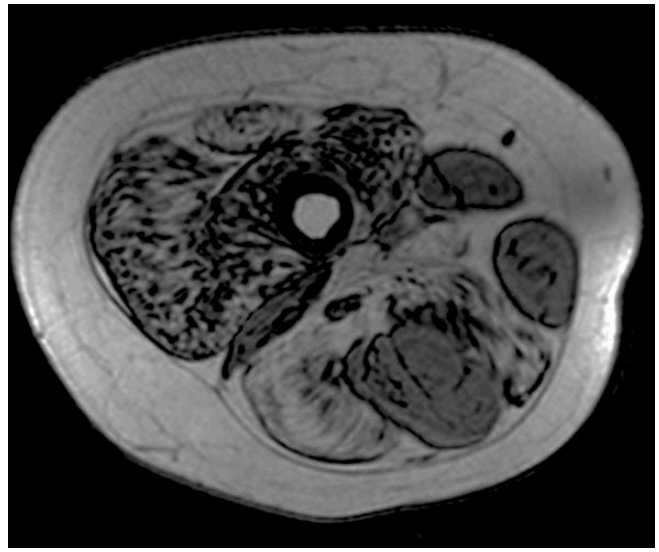
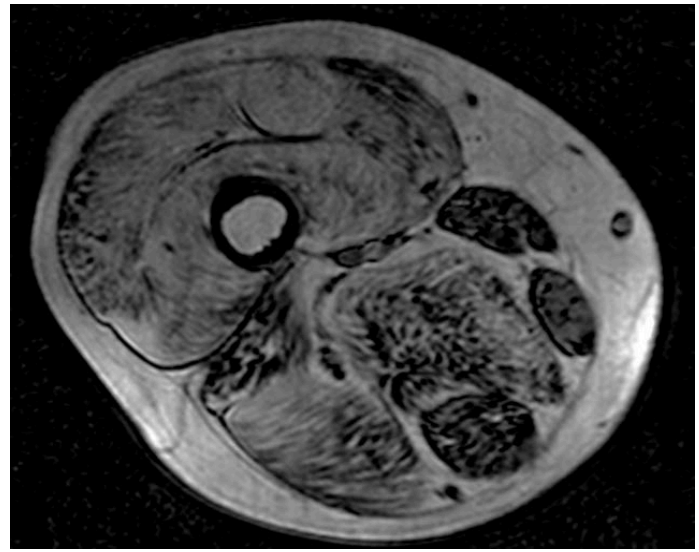
Control

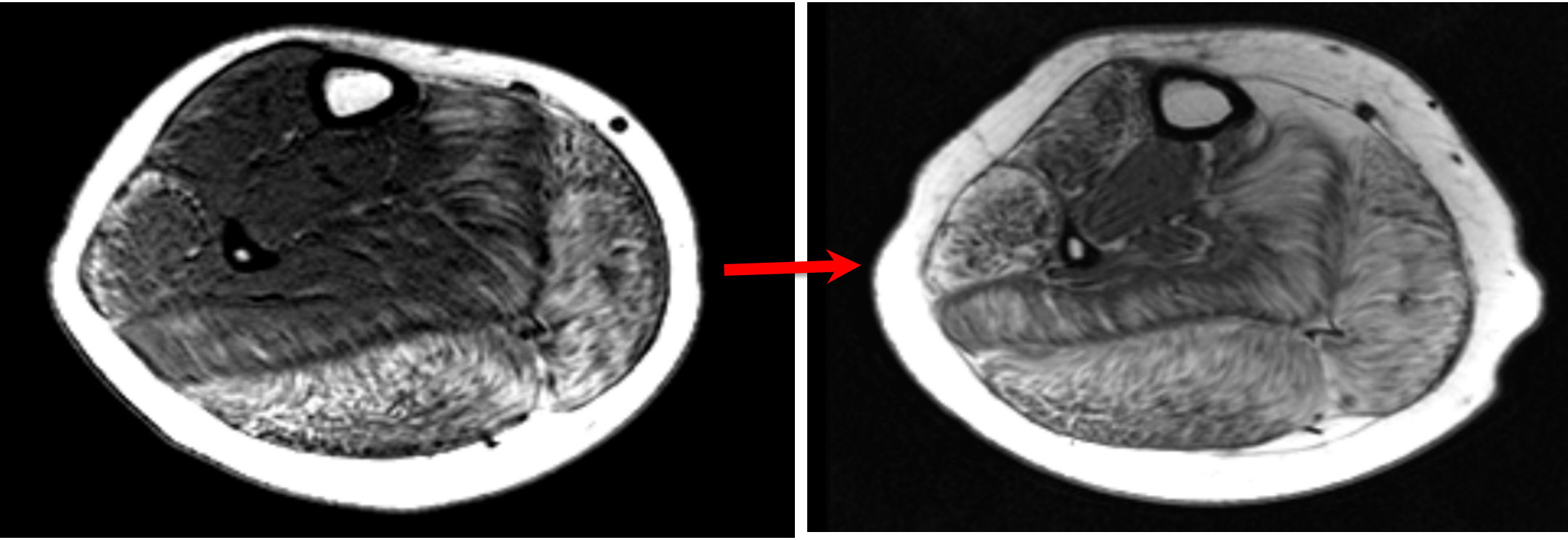


Duchenne

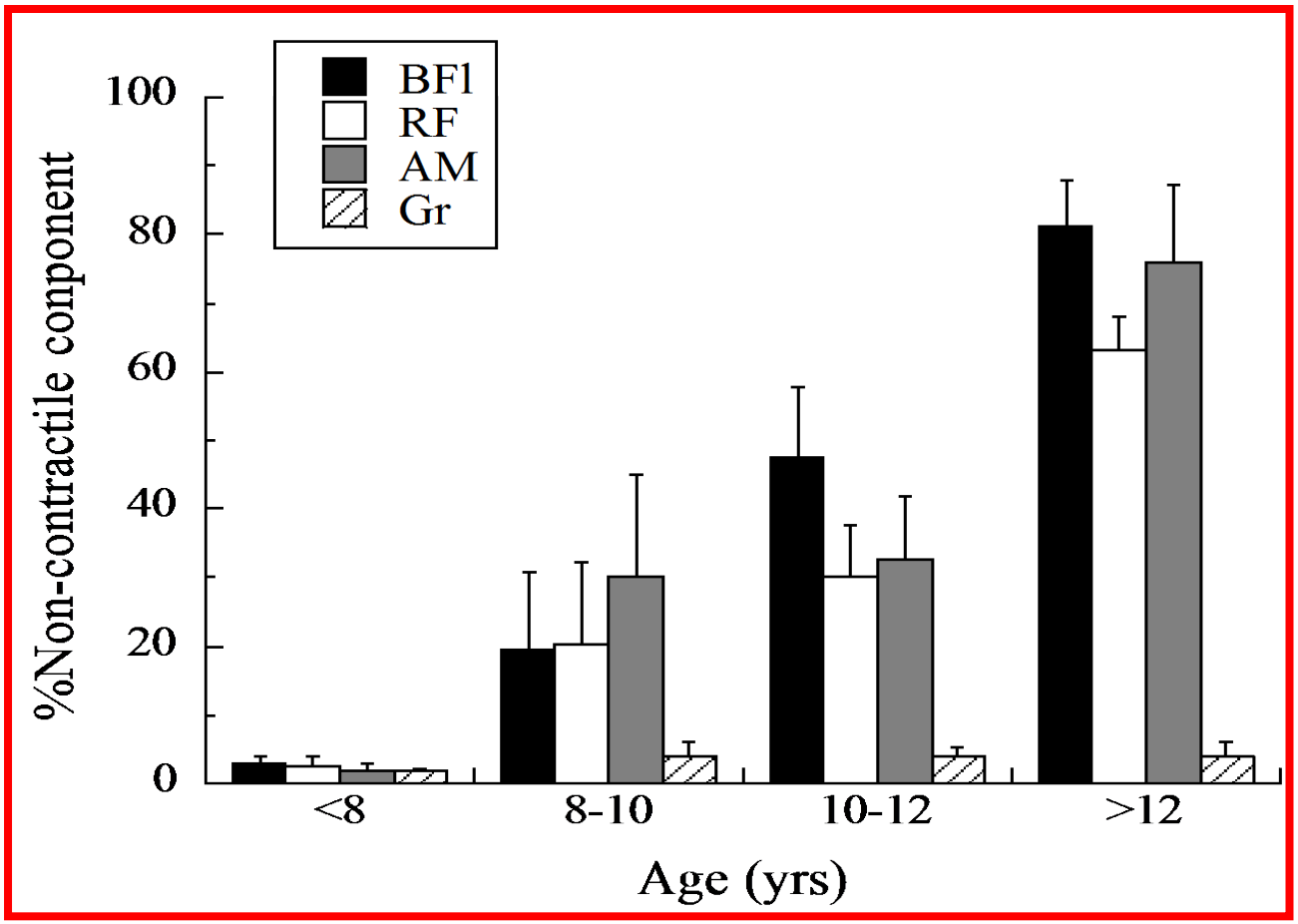


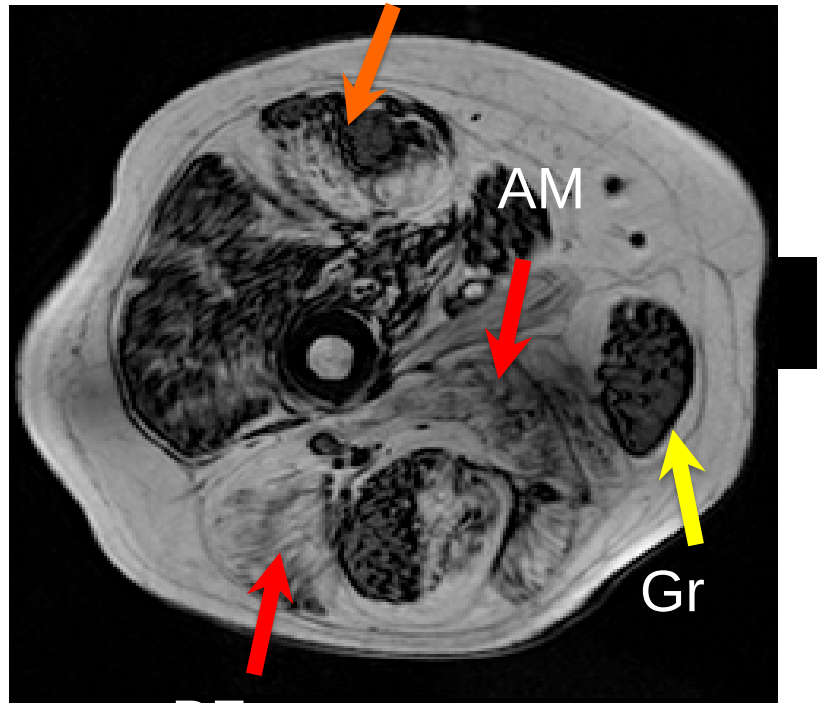
Thigh muscles

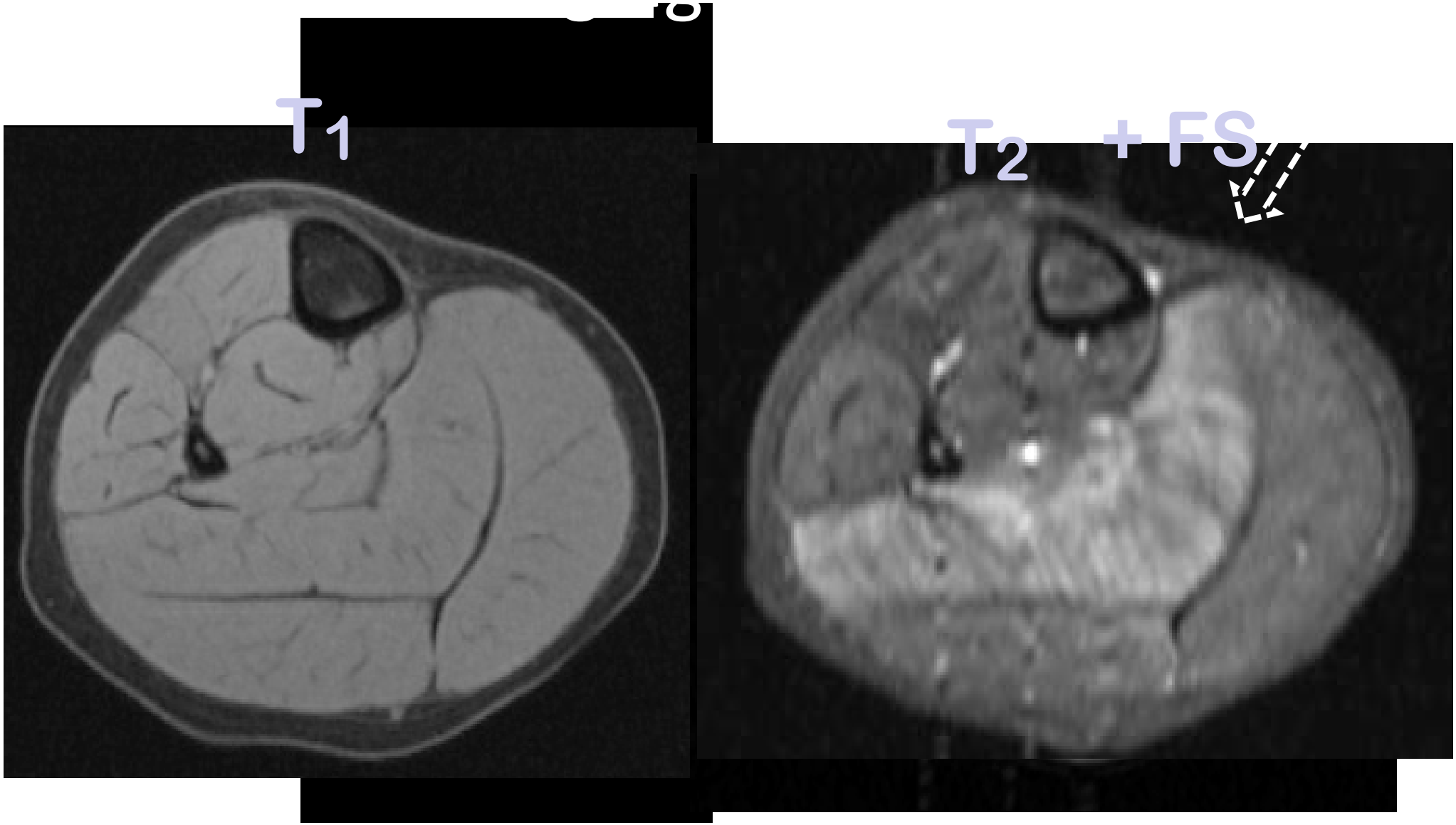









- Specific force production (force/muscle CSA)

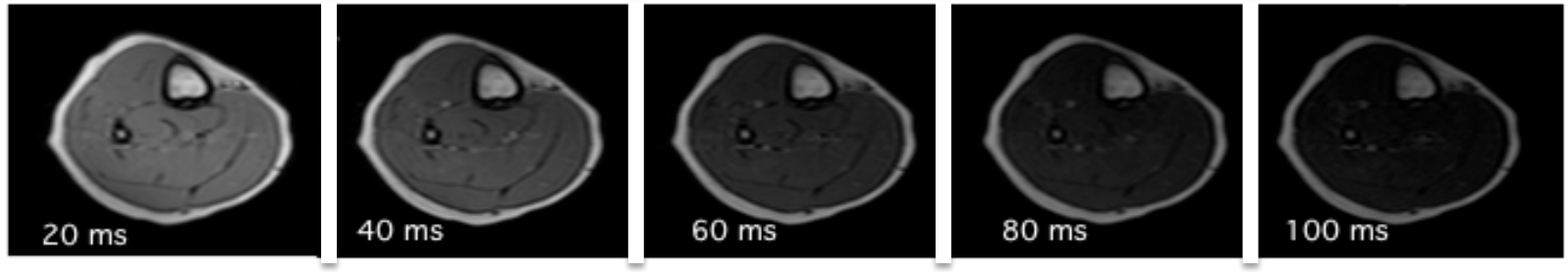

BFl
RF
AM
Gr
100
80
60
40
20
0
%Non-contractile component
<8
8-10
10-12
>12
Age (yrs)

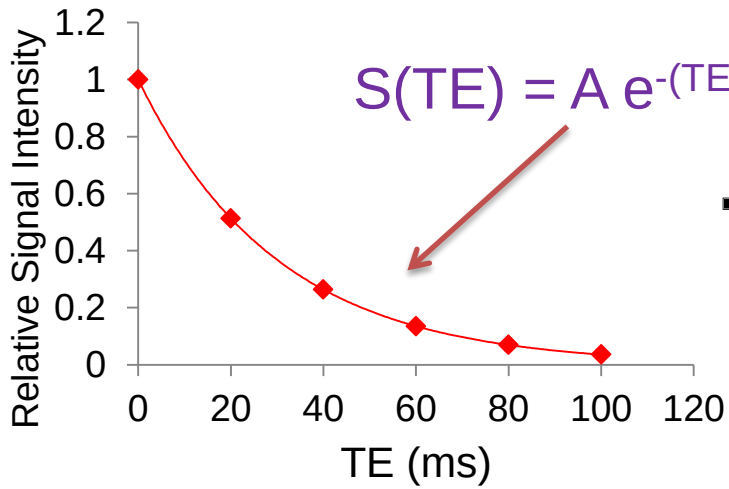

AM
Gr

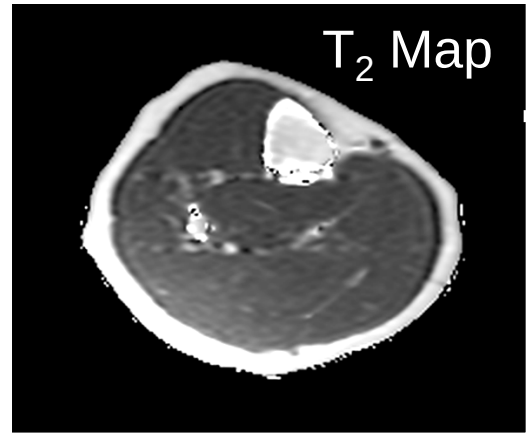

T1
T2 + FS

T_2 as Marker of Muscle Damage/Inflammation

TE=

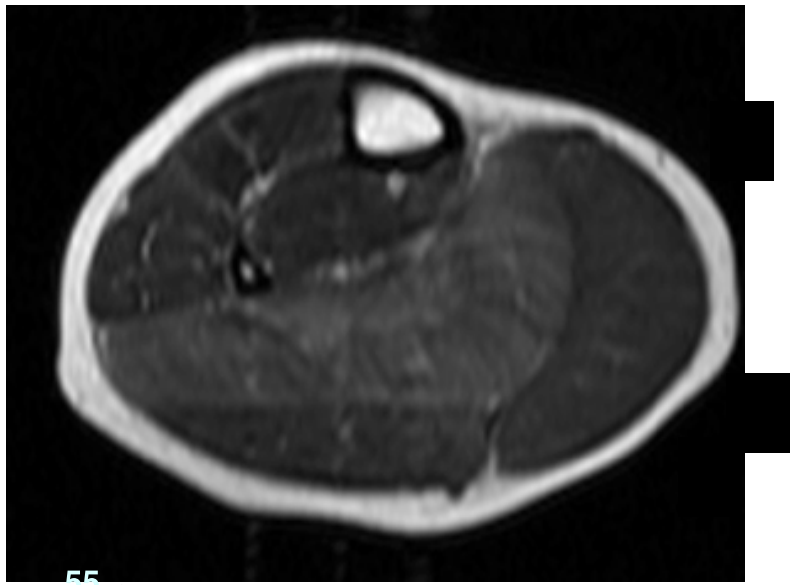


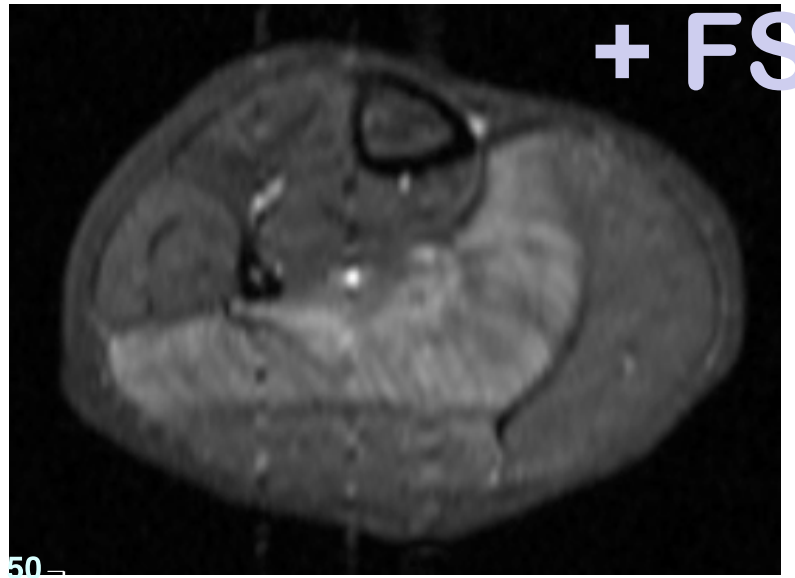


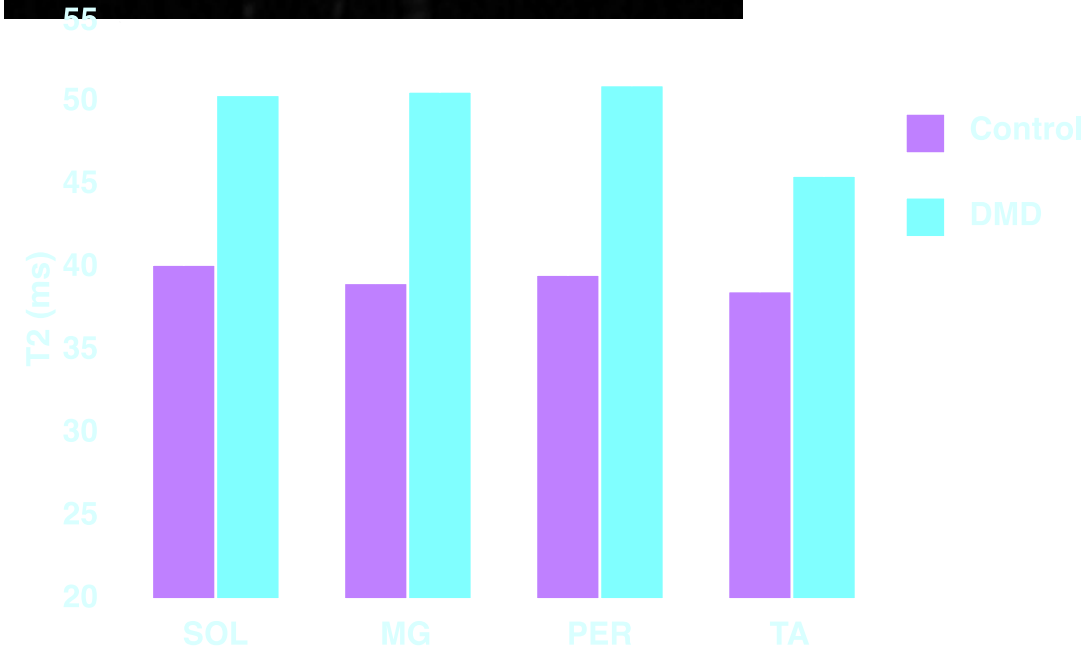


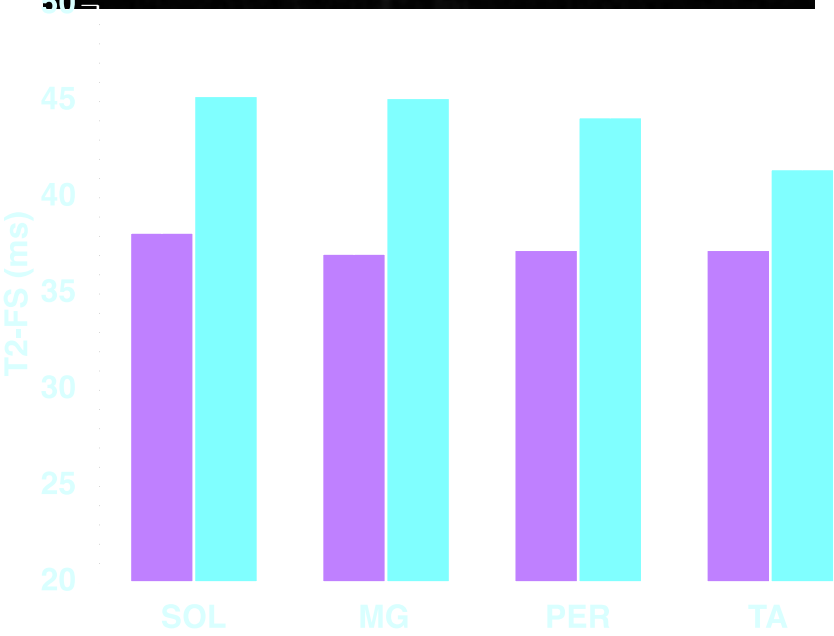
T_2 is very sensitive to local tissue chemistry

- Changes in tissue compartmentation, i.e. membrane permeability
- Water content; edema, inflammation/regeneration
- Fat content, fibrosis,…

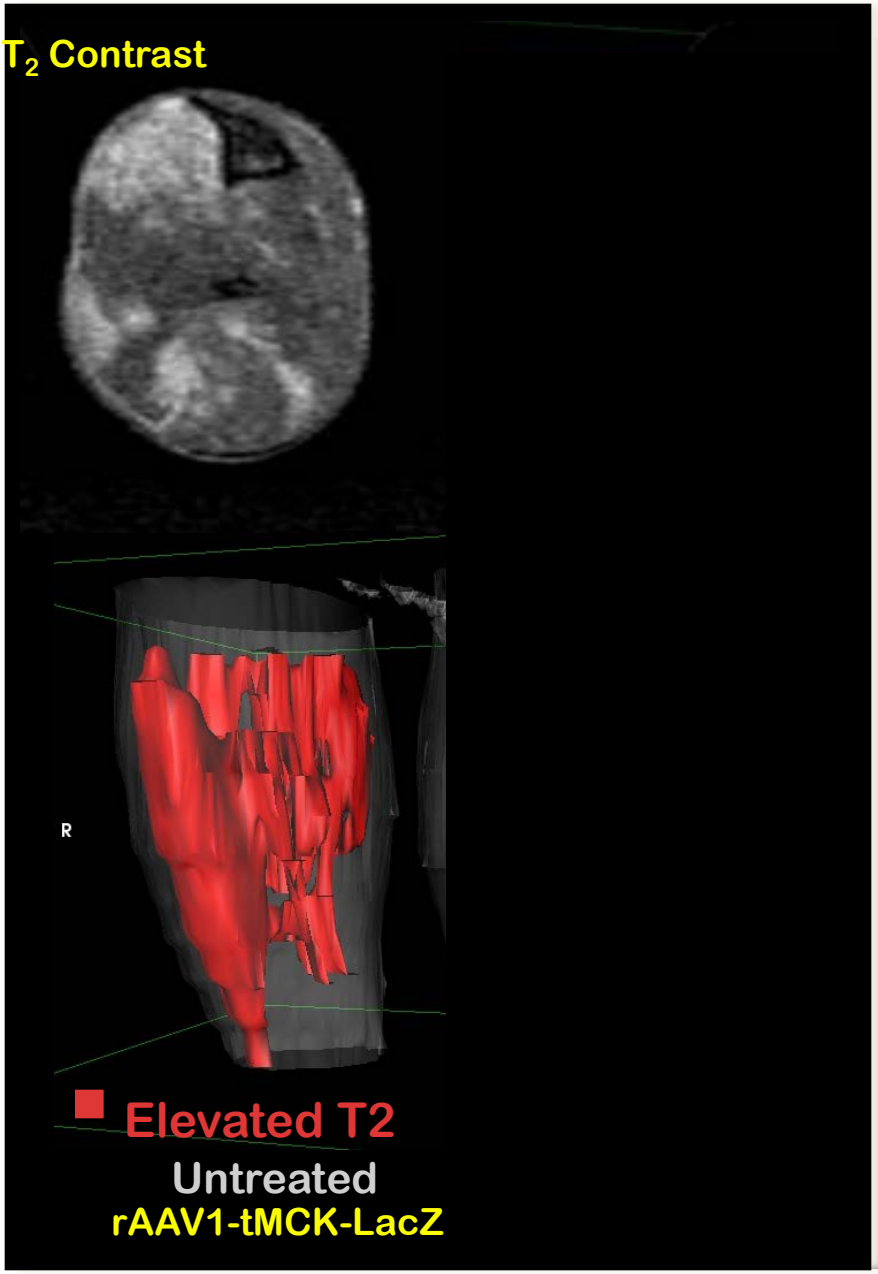


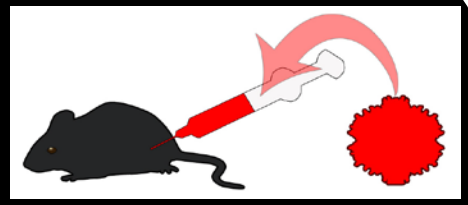

+ FS

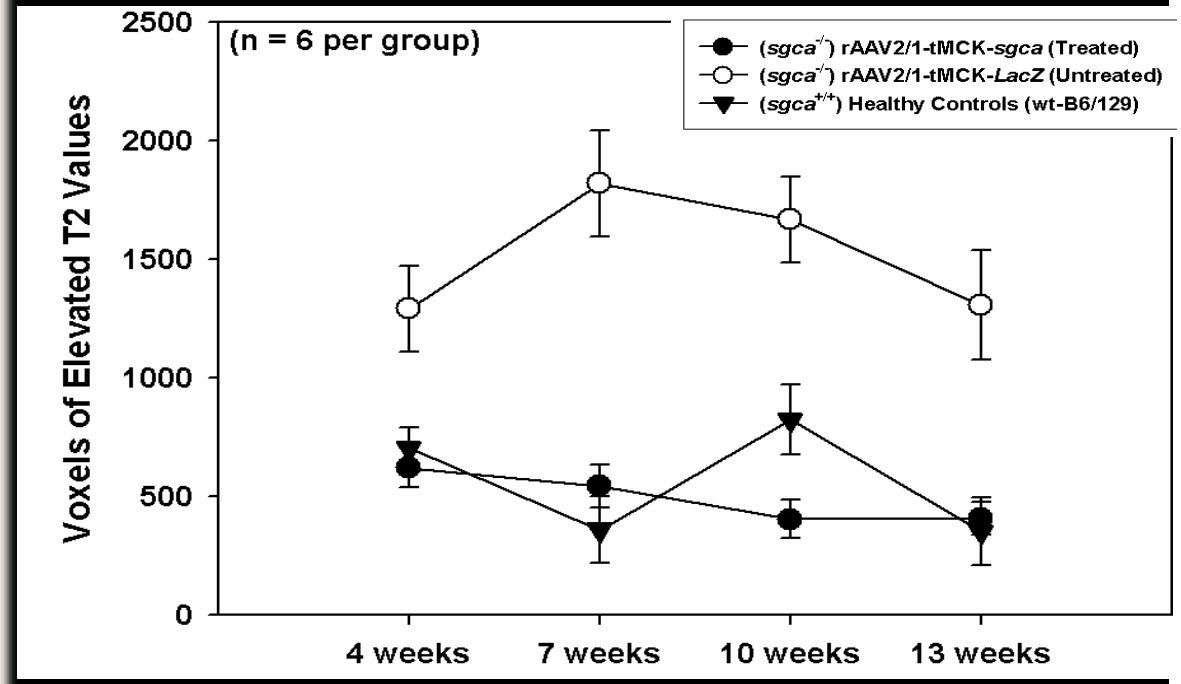

55
50
45
40
35
30
25
20
T2 (ms)
SOL
MG
PER
TA
Control
DMD


50
45
40
35
30
25
20
T2-FS (ms)
SOL
MG
PER
TA

MRI Monitoring Efficacy of Treatment

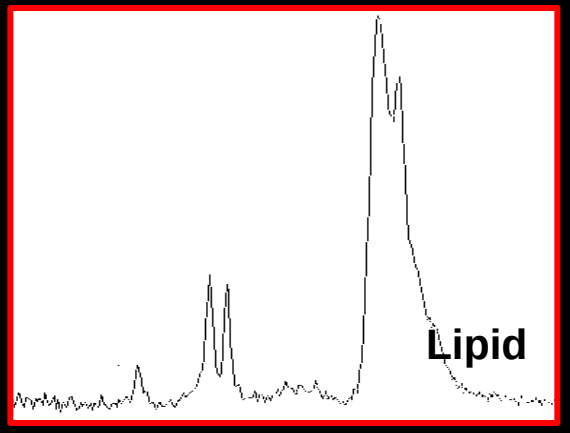




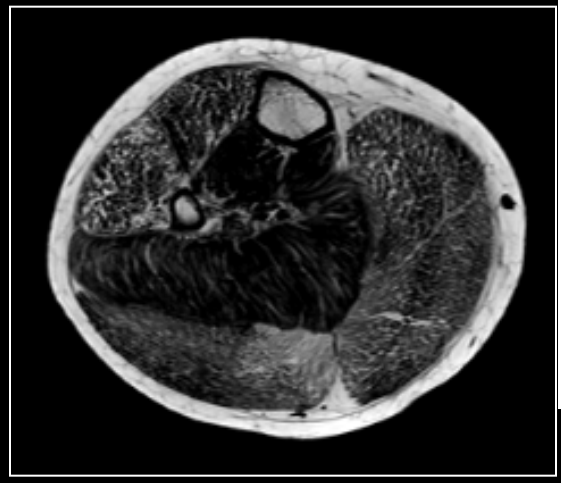


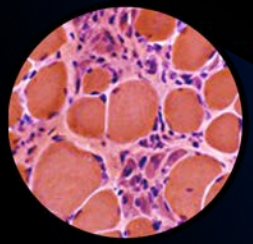
Pacak, *et al* "Long-term Skeletal Muscle Protection After Gene Transfer in a Mouse Model of LGMD-2D." *Mol Ther*. 2007 Oct;15(10):1775-81.

H-Spectroscopy

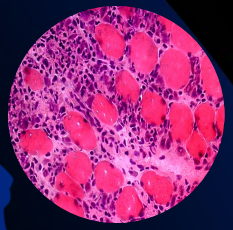


3 point Dixon Imaging

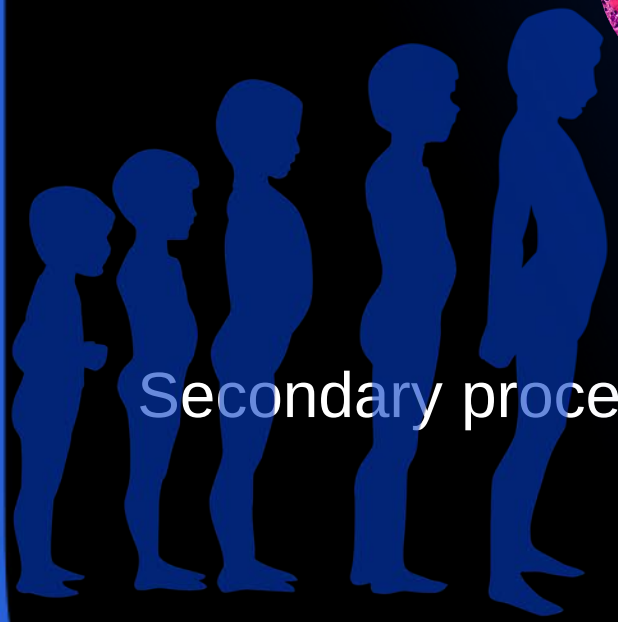




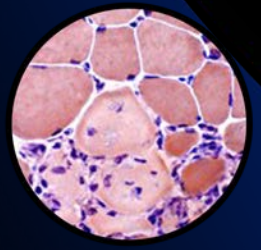
Membrane Integrity



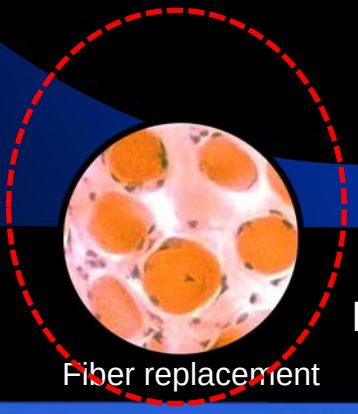
Inflammation



Secondary processes



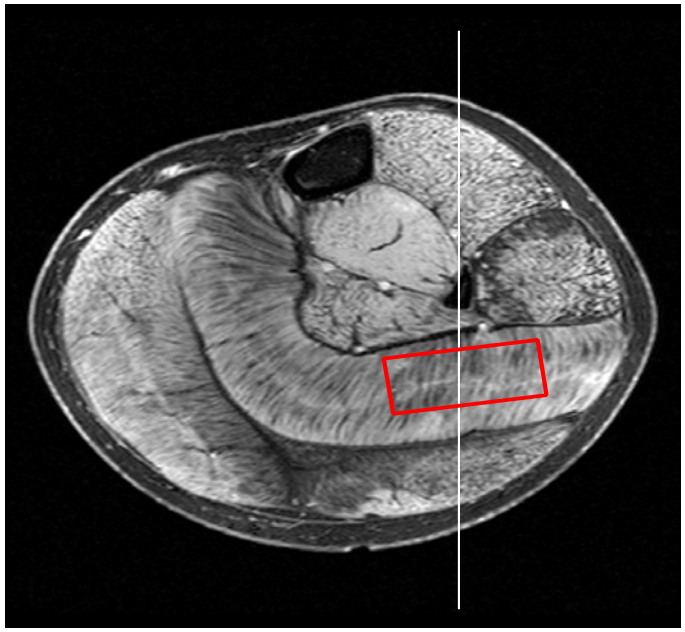
Apoptosis and atrophy

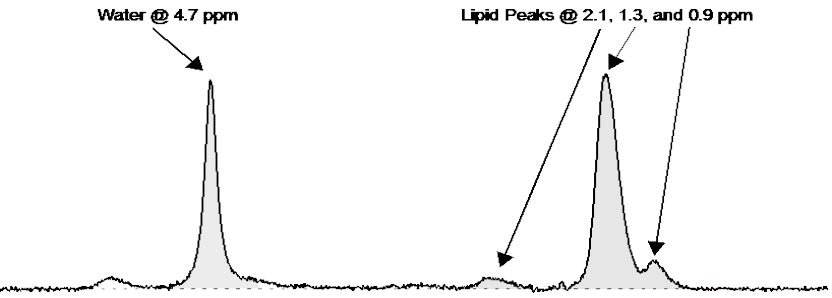


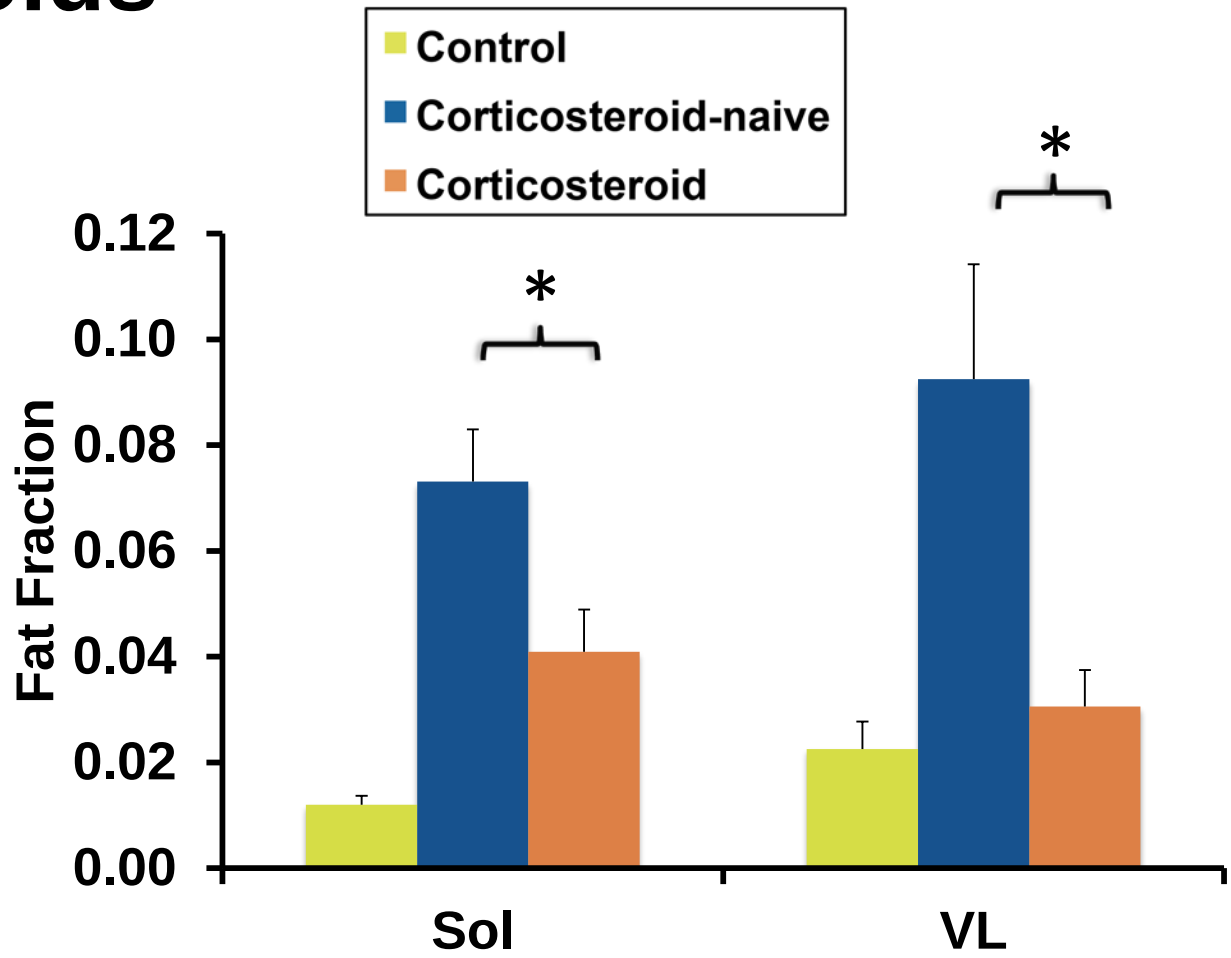
Fiber replacement

Disease Progression

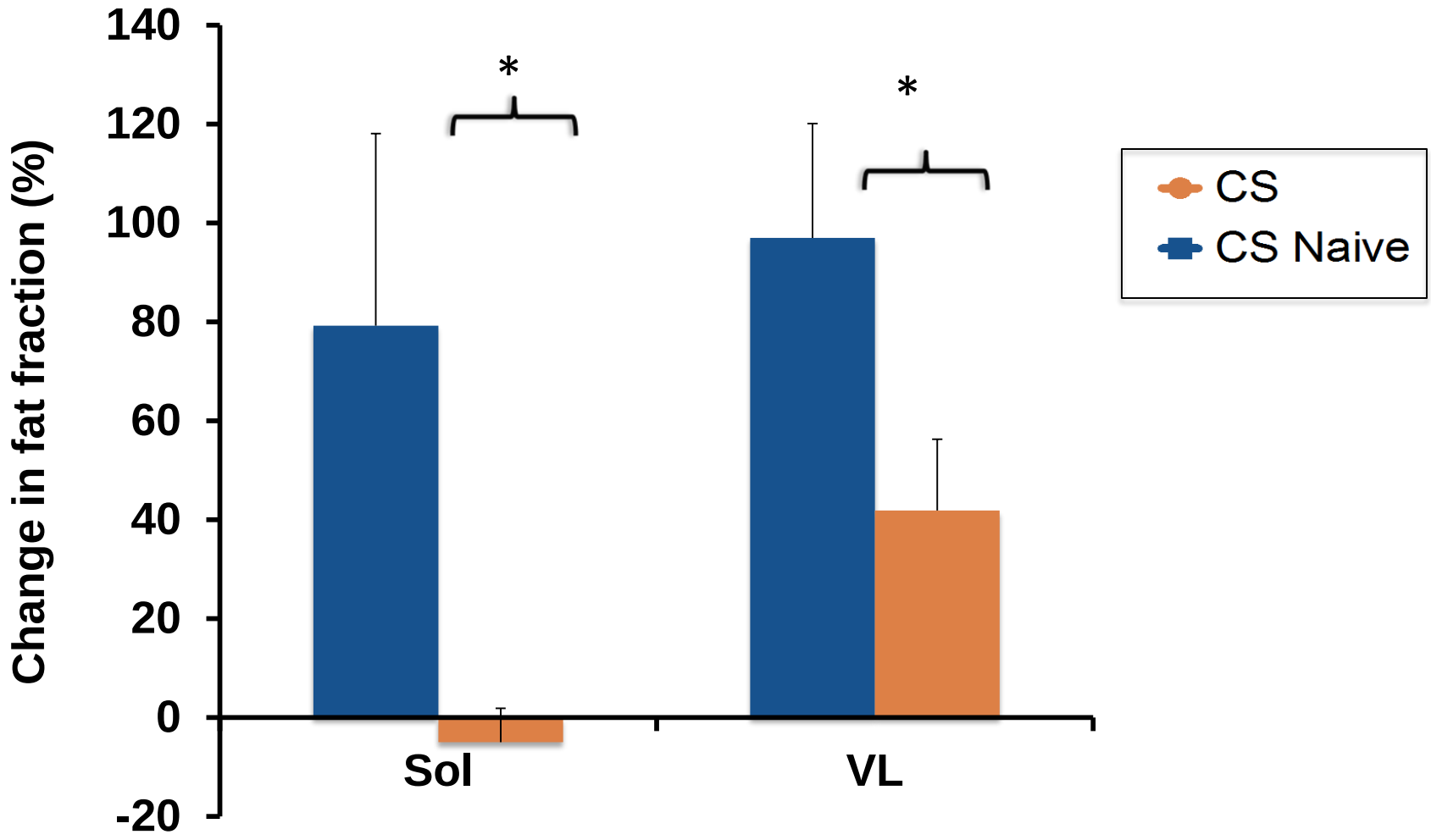
Comparison of Fat Fraction ± Corticosteroids



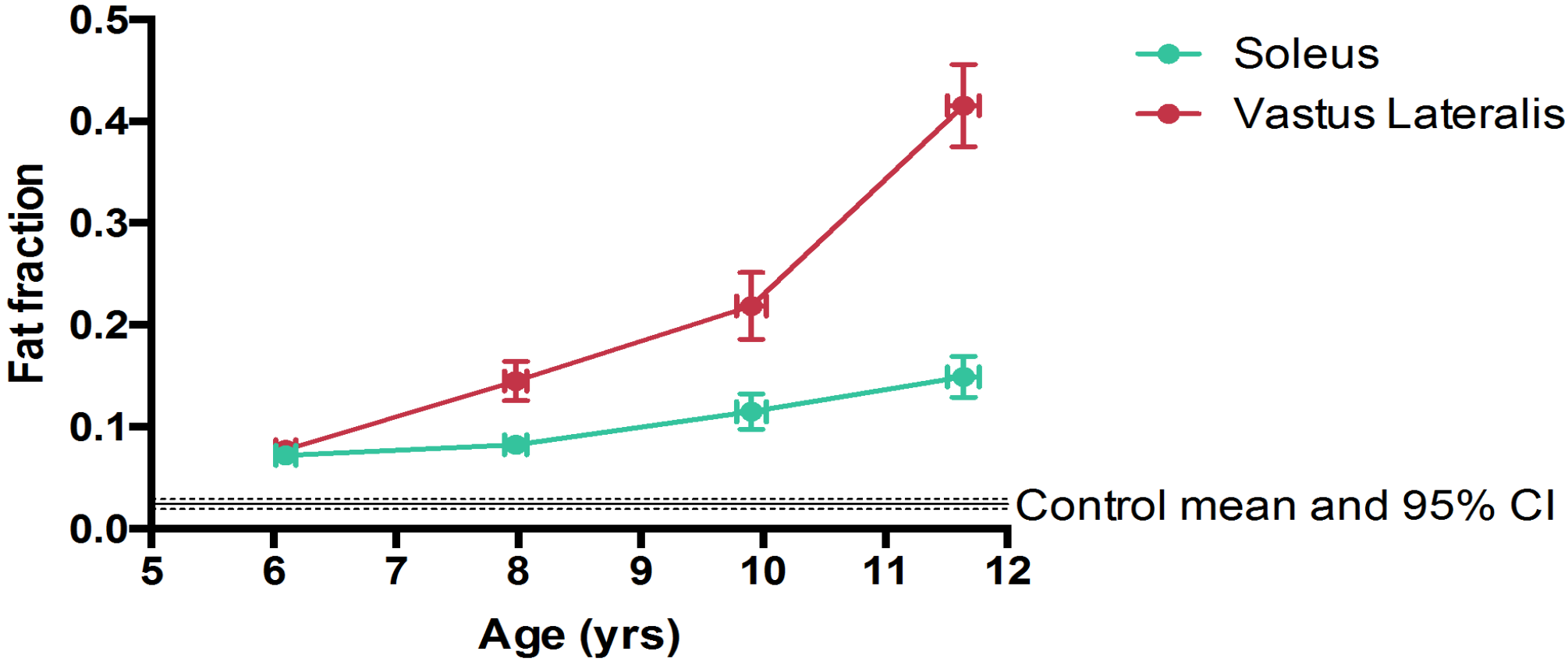




1 year Progression in Fat Fraction ± Corticosteroids



Progression of Fat Fraction with Corticosteroids



How can MRI be useful for dystrophin replacement therapies?

- MRI can identify areas of intact muscle to guide biopsies.
- Dystrophin expression should result in **a slower progression in intramuscular Fat Fraction** compared to untreated patients.
- The initiation of dystrophin expression may be associated with **an acute decline in T_2**, which can be detected by both MRI and ^{1}H-MRS. However, in older boys with high fat fractions, it may be necessary to use ^{1}H-MRS to visualize only the T_2 component specifically due to inflammation and/or damage.