Towards the assessment of metabolic biomarkers and creatine uptake and turnover in skeletal muscles of patients with Facioscapulohumeral muscular dystrophy using MR spectroscopy

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Ethical review	Approved WMO
Status	Pending
Health condition type	Muscle disorders
Study type	Observational invasive

Summary

ID

NL-OMON30391

Source
ToetsingOnline

Brief title
Assessment of biomarkers in FSHD

Condition

- Muscle disorders

Synonym
muscle disease, muscular dystrophy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: FSH society

Intervention

Keyword: Biomarker, Creatine, FSHD, Magnetic Resonance Spectroscopy

Outcome measures

Primary outcome

Normal values for metabolites detectable with 1H and 31P MRS will be determined in healthy volunteers, as well as their reproducibility. Thereafter, these values are compared with the values obtained in FSHD patients, for both affected and not-affected muscle. In the healthy volunteers on creatine supplementation, values for uptake and turnover of creatine will be compared between different skeletal muscles.

This pilot study is considered succesfull if differences in metabolite values are observed between affected and not-affected skeletal muscle. These metabolite values can be used as a biomarker for the severity of the disease in specific skeletal muscles and possbily in the future for the evaluation of therapies. Finally, the values for uptake and turnover of creatine in healthy volunteers can provide a basis for a comparable study in FSHD patients, to determine if creatine supplementation would be a tentative therapy.

Secondary outcome

NA

Study description

Background summary

Fascioscapulohumeral muscular dystrophy (FSHD) is a hereditary neuromuscular condition, mainly characterised by progressive muscle weakness and atrophy of specific skeletal muscles. In FSHD, the skeletal muscles of the face, upper arm and shoulder region are typically affected first while involvement of other skeletal muscles occurs later. At present it is unknown why certain skeletal muscles are involved before others and no treatment is available for patients. Magnetic resonance (MR) techniques can be used to obtain an image of specific locations in the body without the need for invasive procedures or harmfull radiation. MR imaging (MRI) is applied to obtain an anatomic image of different tissues in the body and MR spectroscopy (MRS) can be used to visualize concentrations of specific compounds. The advantage of MR methods is that a subject can be measured multiple times without harm.
Studies of the skeletal muscles of other muscular dystrophies have shown a decrease in creatine related to the severity of the disease [1]. Therefore, in several muscular dystophies creatine supplementation is applied therapeutically [2]. However, it is unclear whether the supplemented Cr is taken up in all skeletal muscles at the same rate and if turnover rates differ between muscles, while this can be important for the format of creatine supplementation. Recently, we developed a method to non-invasively determine creatine uptake and turnover, using 13C MRS and 13C labeled creatine, a non radioactive compound [3].

1. Sharma U et al. 2003 Biochemical characterization of muscle tissue of limb girdle muscular dystrophy: an 1H and 13C NMR study. NMR Biomed. Jun; 16(4):213-23)
2. Wyss, M. and A. Schulze, Health implications of creatine: can oral creatine supplementation protect against neurological and atherosclerotic disease? Neuroscience, 2002. 112(2): p. 243-60
3. Kan HE, van der Graaf, M, Klomp, DWJ, Vlak, M, Padberg, GW, Heerschap, A. Intake of 13C-4 creatine enables simultaneous assessment of creatine and phosphocreatine pools in human skeletal muscle by 13C MR spectroscopy. Magn Res Med. 2006; 56(5): 953-957

Study objective

Untill now, MRS has never been applied to skeletal muscles of FSHD patients. As MRS provides a unique window on several compounds in skeletal muscle and some skeletal muscles of FSH patients are affected by the disease, it is possible that differences in metabolite concentrations are detectable by MRS. Therefore, the goal of the present study is to determine if MR spectra of different skeletal muscles in FSH patients show abnormalities. As different

skeletal muscles in these patients are affected more severely, MR spectra of different skeletal muscles within one subject can be used to obtain information on affected and not or less affected skeletal muscles. The obtained values for FSHD patients will be compared with results from healthy volunteers.
Secondly, creatine uptake and turnover will be studied in different skeletal muscles of healthy volunteers.

Study design

The following MR experiments will be performed at a field strenght of 3 Tesla on FSHD patients as well as healthy volunteers. In healthy volunteers the experiment will be performed twice on separate days to obtain a measurement for reproducibility:

A. MR imaging to obtain an anatomic image of the lower leg (affected - not affected muscle) and determination of the region of interest for MRS
B. 1H MRS for determination of proton detectable metabolites
C. 31P MRS for determintation of phosphorous metabolites

A second group of volunteers will be supplemented with creatine during 5 days and MR experiments will be performed before, during and after this period. The same protocol as described above will be applied, however, in "C" 13C MRS will be spplied instead of 31P MRS.

Study burden and risks

- The subject is positioned on the bed in the tunnel of the MR scanner during the MR experiment and the lower leg is positioned in a dedicated receiver. The subject is allowed to listen to music while inside the scanner, to increase comfort as much as possible. The MR scanner consists of a magnet with a narrow tunnel, in which the subject is positioned with his/her leg, therefore, severe claustrofobia is an exclusion criterium. As the tunnel is not too long, the subjects head can remain outside of the tunnel during the experiment.
- MRS uses non-ionising radiofrequent radiation in combination with a static magnetic field for which the FDA has formulated security guidelines. These guidelines will be followed.
- Creatine supplementation for 5 days in a dose as applied in this study has been shown to not have any adverse effects on health [2].

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

FSHD patients: clinically affected patients with a genetically confirmed diagnosis, moderate severity of the disease, informed consent.
Heatlhy volunteers: informed consent

Exclusion criteria

All subjects: kidney or liverproblems (present or past), diabetes, wheelchair bound. MR contra-indication: pacemaker, cerebral clips, metal splinters, neuro stimulator, cardiac arythmias, epilepsy, severe claustrofobia, pregnancy.
Healthy volunteers: skeletal muscle problems or disease

Study design

Design

Study phase:	2
Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2007
Enrollment:	35
Type:	Anticipated

Ethics review

Approved WMO

Date:	14-05-2007
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2006-006776-37-NL
CCMO	NL14741.091.06