HEALTH-2007-2.4.5-10: Understanding and combating age related muscle weakness *MYOAGE*

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

Summary

ID

NL-OMON34394

Source
ToetsingOnline

Brief title
MYOAGE

Condition

- Muscle disorders

Synonym
Age related muscle weakness, Sarcopenia

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Myoage FP7 program HEALTH-2007-2.4.5-10

Intervention

Keyword: Ageing, Sarcopenia

Outcome measures

Primary outcome

PHASE I

Muscle biopsies: Myoblastic proliferative capacity; muscle histology: number of satellite cells, proportion of the different types of fibres and the volume of fibres as well as the number of nuclei/fibres, proportion between fibres to adipocytes;, protein/RNA/DNA characteristics

Percutaneous muscle biopsy will be used to compare with muscle material taken by open surgery (if comparable).

Blood: Haematological measurements (Hb, MCV, Leukocytes, Thrombocytes), cytokine assays, PBMCs, LPS/Pam3Cys whole blood stimulation assays, CRP, albumine, kreatinine, GH, IGF-1 and BMP-4, pro as well as anti inflammatory cytokines (IL-12, IFNγ, IL-6, TNFα) Number of B cells, T cell subsets, monocytes and natural killer cells. Naïve, memory and regulatory T cell subsets.

Skin and fat biopsies: proliferative capacity (comparison with myoblasts); skin histology: number of senescent cells (comparison with myoblast culture and muscle histology), inflammatory phenotype (comparison with blood stimulation and stimulation of myoblasts), protein/RNA/DNA characteristics (comparison with muscle tissue).

Anthropometric measures Length, arm span, weight and waist circumference.

PHASE II

Blood: haematological measurements (Hb, MCV, Leukocytes, Thrombocytes), cytokine assays, PBMCs, LPS/Pam3Cys whole blood stimulation assays, CRP, albumine, kreatinine, Calcium, Vitamin D, GH, IGF-1 and BMP-4, pro as well as anti inflammatory cytokines (IL-12, IFNγ, IL-6, TNFα) Number of B cells, T cell subsets, monocytes and natural killer cells. Naïve, memory and regulatory T cell subsets; glucose tolerance (mmol/L),

Questionnaires: QoL; present and past education, employment and levels of physical activity, medical history and current medication. ADL dependency

DEXA: Muscle mass/ fat content of the upper and lower limbs; bone mineral density

Lungfunction: FEV1 (L/s), FEV (L), FEV1/FEV ratio (%), Total lung capacity (L), Tidal Volume (L)

Grip strength (Kg)

Gross Physical performance: Ground reaction force (during jump), TUG, 40m walk test (s)

Balance: body sway (mean displacement body centre of mass, mm)

Kinematics (accelerometry/gyroscopy): angles with respect to gravity field (degrees), accelerations I x-y and z directions

AGE: skin autofluoresence (arbitrary units)

MRI: ventricle size, quantity of White matter lesions, hippocampus volume

Cognitive function: speed of processing, learning and memory, executive function and attention

Quadriceps muscle performance: Quadriceps strength (N) at MVC (max voluntary

contraction); stimulation current (mV) to reach 25% MVC, failure time

sustaining 50% MVC (s); m vastus lateralis pennation angle (degrees).

Haptic robotics: neuromechanical performance around the wrist: viscosity

(Nms/rad), stiffness (Nm/rad), reflex torque (Nms/rad), short range stiffness

(Nm/rad)

Needle biopsy m vastus lateralis: pro- and anti-inflammatory cytokines,

myblasts myotubes, satellite cells mRNA level, post-translational maturation

and localization of myostatin, fiber size, fiber type

Secondary outcome

Not applicable.

Study description

Background summary

Sarcopenia is a universal, age-related loss of muscle mass associated with a loss of strength and function resulting in muscle weakness. It often leads to progressive disability and loss of independence (Lauretani et al. 2003). The development of sarcopenia has also been associated with increased morbidity and mortality (Rantanen et al. 2003, Ling et al. 2010). The onset and dimension of the age related decrease in muscle mass and strength are muscle dependent and heterogeneous and it can occur as early as 30 years of age and results in a loss of about 30-50% of the muscle mass by the age of 80 years (Evans et al. 1997; Beenakker et al. submitted).
Despite its clinical importance, the pathophysiology leading to sarcopenia is not well understood. Environmental factors, such as a sedentary life style and malnutrition contribute to sarcopenia; other possible causes of sarcopenia include systemic changes such as a decreased growth hormone production and increased inflammatory cytokine secretion (Morley et al. 2001).
On the cellular level, the age associated decline in muscle mass and function results from the loss of muscle fibers, especially the type II fibers (Lexell et al. 1995), as well as a loss of the cross-sectional area of remaining fibers (Vandervoort et al. 2002). The number of sublaminar (CD 34+) satellite cells, the muscle fiber progenitor cells capable of self renewal and sufficient for postnatal muscle growth and repair, and the proliferative capacity of these

cells is inversely related with chronological age (Renault et al. 2000; Sajko et al. 2004; Widmer et al. 1995). Additional factors related to the decline in muscle mass is a lower supply of nutrients through diminished vascularisation and arteriosclerosis as well as a decreased efficiency of metabolism of the nutrients and muscle changes due to chronic inflammation. Epidemiological studies have shown a correlation between high levels of inflammatory cytokines (TNF-α and IL-6), a low level of IGF-1, high levels of oxidative stress, decreased mitochondrial function and sarcopenia. Recently, our group was able to show that a high innate production capacity of TNF-α preceded a steeper decline in muscle strength over time within a population-based prospective follow up study (Taekema et al. 2007). However, in this study the underlying cellular and molecular mechanisms cannot be identified.

Study objective

The aim of the represent proposal is twofold,
1. [PHASE 1] the establishment of a human tissue biobank including muscle and blood, and additionally from a subset subset of subjects fat and skin biopsies will be taken. Samples will be distributed throughout the consortium Myoage (1) for the optimisation of all protocols to be able to translate basic biological data obtained with model organisms/systems to human material, (2) the understanding of the various biological mechanisms involved in sarcopenia, (3) intraindividual mechanisms related to human ageing, studied in different types of human tissues.
2. [PHASE 2] studying the contribution of quantity, quality and control of muscle make to loss of mobility and quality of life in an elderly population being highly and less active, together with a control group. A total of 525 subjects will be recruited in five European centers (each recruitment center 105 subjects in total, 35 subjects in each group). Leiden is one of the recruitment centers. Subjects will be phenotype on functional, imaging and cellular level. All recruitment centers use the same protocols / measurements.

Study design

PHASE 1.1.
Observational, cross sectional study. Inclusion of 55 patients undergoing knee replacement and 105 patients undergoing hip replacement either because of a primary locomotor disease or
PHASE 1.2.
Observational, cross sectional study. Inclusion of 20 patients undergoing knee replacement
PHASE 2:
Observational, cross sectional study. Inclusion of 105 healthy subjects, divided over three groups: healthy young, sedentary old, active old.

Study burden and risks

PHASE 1:
Patients are under general anesthesia and undergoing hip or knee surgery. Muscle tissue samples are taken from the distal part or proximal part of m. vastus lateralis, which will be within the operation area. Blood will taken during the operation. Additional fat and skin biopsies will be taken from the operation area. No additional risk or burden is involved.
PHASE 2:
Subjects are invited to the LUMC to perform a number of tests, clustered over two days. The tests include maximal performance, i.e. lung function, 6 meter walk test and maximal quadriceps strength. The maximal performance tests are spread over two days. The order of the test battery is such that physically and mentally strenuous tasks are separated by passive tasks. The test battery includes one invasive procedure, i.e. the needle biopsy.
1) Quadriceps dynamometry is performed in an isometric testing chair in which the subject is positioned upright. The test is isometrically, i.e. static performance without any moving (parts). The electrical equipment of the chair consists of a low voltage force transducer. The maximal force tasks may result in some muscle soreness which may last for one or two days.
2) Electrical stimulation is performed using commercially available stimulating devices which meet all required certifications. Muscle stimulation is performed at a low intensity (max 50% of MVC output). EMG-NMS is non-invasive and does not have side effects.
3) Haptic robotics. A commercially available robot manipulator is being used, meeting CE certification. Electrical parts are yielded from the subject. An isolation transformer is applied. The machine is safeguarded against unwanted displacements both by software and hardware boundaries.
4) Spirometry is a routine lung function assessment bearing no risks or side effects
5) The needle biopsy is performed using hollow needle, thickness 3 mm which is 4cm inserted into the m. vastus lateralis muscle. The burden of the procedure is comparable to a widely applied procedure as taking skin biopsies. Before biopsy, the skin is cleaned and anesthetics are applied. The rate of bleeding after taking the biopsy and infection is neglectable. Some but not all patients, experience some pain at the moment the biopsy is taken (like myalgia). Sometimes a small haematoma will develop, although in our 3 previous studies (Jazet IM et al 2008; Jazet IM et al, 2005; Hammer et al, 2008) none of the patients developed this. Furthermore the patient might experience a heavy feeling in the involved muscle the next 24-48 hours. The procedure is applied by an experienced medical physician.
6) Ultrasound is applied by fully certified equipment. No risks are involved.
7) DEXA scan applied by fully certified equipment. No risks are involved.
8) Force plate: the force plate on which subjects stand to assess balance and perform the vertical jumps is integrated in a platform of sufficient size (1 square meter approximately) to prevent subjects from falling off.
9) MRI scan is applied by fully certified equipment. No risks are involved.
10) Insertion of an IV needle is performed by experienced and qualified personnel. The IV needle will remain in situ for about 2,5 hours (time to

complete OGTT test). Risks of this (routine) procedure are minimal.

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

PHASE 1:
Inclusion:
•patients undergoing either total knee replacement or knee periarticular reconstruction (fracture repair, corrective osteotomy, capsular ligament reconstruction) that provide for an open surgery in the lateral part of distal femur; or total/partial hip replacement or proximal femur osteosynthesis.
PHASE 2:
Inclusion:
• healthy young: age ranges 18-30 years;

• elderly: age 70-80 years, free living, ADL independent

Exclusion criteria

PHASE 1:;Exclusion:
• patients less than 20 years
• patients that underwent previous open surgery in parts concerned the biopsy collection
• patients with rheumatoid diseases (RA, polymyositis, dermatomyositis etc)
• patients that undergo insulin therapy
• patients with haemocoagulative syndromes in which collection could cause strong bleeding
• patients with serious neuromuscular disease (flabby and spastic paralysis of legs, myasthenia, myodystrophia
• patients with serious hepatorenal failure
• patients with serious infectious disease and active malignant neoplasia
• patients with serious psychiatric disorders, chronic abuse of alcohol and drugs
• patients that use steroidal medicines
• patients unable to give a personal consent
• Participating in other ongoing research projects.;PHASE 2:
Exclusion:
• Participating in other ongoing research projects.
• patients unable to give a personal consent
• walking distance 250m and less;
• MMSE 23 and lower;
• GDS 5 and higher;
• institutionalized;
• comorbidity: neurological disorders (stroke, M. Parkinson, dementia, muscle disease), metabolic diseases (insuline dependent DM), arthritis: rheumatoid arthritis, severe (pain and functional limitation) osteoarthritis (hip and knee), cancer: diagnosis and treatment of cancer within the last year, polymyalgia rheumatic, heart failure (NYHA 3-4), COPD (Gold 3-4), chronic pain syndrome (fibromyalgia, complex regional pain syndrome etc); haemocoagulative syndromes in which biopsy could cause strong bleeding.
• medication: immunosuppressive drugs (e.g. prednisone, methotrexat, biologicals (TNF-alpha antagonists etc)), insulin, anticoagulantia, e.g. coumarines, carbaspirin calcium.
• fracture last year;
• hip and knee replacement in medical history last 2 years;
• hip and knee replacement causing pain and physical limitation;
• amputation;
• immobilization for 1 week during the last 3 months;
• sports on a highly competitive level
• severe hearing impairment.
• severe visual impairment ..

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-07-2010
Enrollment:	265
Type:	Actual

Ethics review

Approved WMO

Date:	31-05-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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
CCMO	NL32050.058.10