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Investigating the effects of strength training and de-training in young and older men on changes to DNA that affect which genes are active

Submission date
19/12/2019

Recruitment status
No longer recruiting

Registration date
21/12/2019

Overall study status
Completed

Last Edited
06/09/2021

Condition category
Musculoskeletal Diseases

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
As we age, muscle strength and muscle mass is lost. Performing strength training helps in maintaining or slowing down the loss in strength and muscle mass by aging. What is not well known is how mechanisms in the genetic material (like methylation) of the muscle cells helps in this training response, what happens when you stop training, and how you can gain even more strength when you decide to start (re-)training. The aim of this study is therefore to clarify the temporal and dynamic aspects of epigenetic changes caused by strength training in blood and muscle tissue. For that reason the researchers are looking for differences in the methylation profile after training.

Who can participate?
Healthy older (aged 60 and over) and younger men (aged 18-25)

What does the study involve?
Participants undergo a training, de-training and retraining intervention. A small group in the older participants serves as a control group - they don't do the training but are measured in the same way as the participants in the training intervention. The training protocol consists of 12 weeks of high-intensity strength training. The detraining period consists of either a 12-week rest period for the older participants or a two-week immobilisation of one leg for the younger participants.

What are the possible benefits and risks of participating?
Participants may benefit from the strength training in gaining strength and possibly muscle mass. For the participants who will also have muscle biopsies taken, there are some risks involved (some local pain, bruises, infection), but a local anaesthetic will be used. Blood sampling has only limited risks involved. All training sessions are supervised.

Where is the study run from?
KU Leuven, Faculty of Movement and Rehabilitation Sciences (Belgium)

When is the study starting and how long is it expected to run for?
May 2016 to September 2017

Who is funding the study?
Research Foundation Flanders (FWO)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
S59380

Study information

Scientific Title
Role of epigenetics in (de-)training induced responses in skeletal fitness

Acronym
EPIK

Study objectives
This study aims to investigate the role of methylation changes in DNA of muscle biopsies and blood in response to strength training, detraining and retraining in relation to a possible muscle memory phenomenon.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 22/09/2016, Commissie Medische Ethiek, UZ KU Leuven/Onderzoek (Commissie Medische Ethiek, UZ/KU Leuven / Onderzoek, U.Z. Gasthuisberg, Herestraat 49, B 3000 Belgium; Tel: +32 (0)16 34 86 00; Email: ec@uzleuven.be), ref: S59380

Study design
Single-centre non-randomized partially controlled interventional study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Other

Study type(s)
Other

Participant information sheet
Not available in web format, please use the contact details below to request a participant information sheet

Health condition(s) or problem(s) studied
Muscular fitness, sarcopenia

Interventions
This study is a non-randomized, 12-week incremental resistance strength training study, followed by a 12-week detraining period (in older subjects) (or 2-week casting in young subjects) and a retraining phase (12 weeks resistance strength training). The focus is on the temporal and dynamic aspects of epigenetic changes caused by strength (de-/re-)training in blood and muscle tissue.

Participants completed 12 weeks of RT (training), followed by two weeks of immobilization by means of a full leg cast (detraining) in the young participants. The older group did not perform any strength training during 12 weeks. Hereafter, participants participated again in a 12-week RT

period (retraining). Knee extension strength and muscle biopsies of the m. vastus lateralis were obtained before training (Week 0), after training (Week 12), after detraining (young: Week 14 or old: Week 24) and after retraining (young: Week 26 or old: Week 36).

Resistance training program (training and re-training phase)
During 12 weeks, participants followed a supervised RT program for the upper and lower body with three sessions per week on non-consecutive days (compliance rate > 80 %). Each training session lasted approximately 60 min, including a dynamic warm-up and cool-down phase. The following exercises were included: 45° leg press (plate loaded linear leg press, Life Fitness Signature Series), seated barbell shoulder press, dumbbell bent-over row, 45° calf press (plate loaded linear leg press, Life Fitness Signature Series), abdominal crunches, barbell bench press, leg extension (Life Fitness Optima Series) and barbell biceps curl. Subjects performed the exercises in the order described above with the first exercise varying each RT session. Training intensity of load was gradually increased from ~65 % of 1RM to ~80 % of 1RM with sets and repetitions ranging between 2 – 3 and 8 – 15 respectively. The same RT program was used for the training and retraining phases of the study.

Detraining
In young participants: To stimulate muscle atrophy, the right leg was immobilized with the knee in nearly full extension for two weeks using a full leg cast (foot included). Subjects were asked not to put weight on the casted leg. To prevent deep vein thrombosis, anticoagulant enoxaparin (40 mg per 0.4 ml per day, Clexane®, Sanofi Belgium, Diegem, Belgium) was administered daily via subcutaneous injection into the abdominal skinfold. In older participants: participants stopped RT during 12 weeks.

All evaluated primary and secondary outcome measures were taken at all indicated timepoints (baseline: week 0, training: week 12, detraining: week 14/24 and retraining week 26/W36). Muscle biopsy collections were performed 72 h after the last RT session in week 12 and week 26 /W36).

Intervention Type
Behavioural

Primary outcome measure
DNA methylation patterns in blood and muscle tissue analysed using Infinium MethylationEPIC BeadChip microarray (850K; Illumina Inc., CA, USA) at weeks 0, 12, 14/24 and 26/36

Secondary outcome measures
1. mRNA expression of genes identified to show differentially methylated CpG sites during training responses assessed using RNASeq at weeks 0, 12, 14/24 and 26/36 (in muscle biopsy samples)
2. Satellite cell and myonuclei cell count assessed using Laminin, Pax7 and PCM1 staining (immunohistochemistry) at weeks 0, 12, 14/W24 and 26/36 (in muscle biopsy samples)
3. Muscle fiber type specific area/minimum Feret diameter changes assessed using MHC-I, MHC-IIa, MHC-IIx staining (immunohistochemistry) at weeks 0, 12, 14/24 and 26/36 (in muscle biopsy samples). For all stainings, images were captured with a Zeiss AxioObserver Z1 Fluorescence Microscope (10x objective for fibre typing and SC content, 20x objective for myonuclear content), using Zen blue software from Zeiss. For fibre size and fibre type analysis, the researchers included 230 ± 32 fibres (mean ± SD) per subject per time point. Myovision Basic was used for the quantification of fibre type distribution and minimum Feret diameter.
4. Strength measures of the knee extensors/flexors (static, dynamic, isotonic) assessed using

Biodex Medical System 3® dynamometer (Biodex Medical Systems, Shirley, NY, USA) at weeks 0, 12, 14/24 and 26/36
5. Anthropometry: stature, body weight, BMI, arm, thigh, calf, waist circumferences (tape), skinfolds (subscapular, suprailiacal, calf, thigh, triceps, biceps)(Harpenden Caliper) at weeks 0, 12, 14/24 and 26/36
6. Body composition measured using bio-electric impedance at weeks 0, 12, 14/24 and 26/36
7. Epigenetic age based on methylation in DNA of blood and muscle tissue assessed using the Horvath's Clock calculator (https://dnamage.genetics.ucla.edu/home) at weeks 0, 12, 14/24 and 26/36

Overall study start date
01/05/2016

Completion date
30/09/2017

Eligibility

Key inclusion criteria
For the older group:
1. Age >60 years
2. Male
3. No contra-indications for participation in strength training
4. No contra-indications for muscle biopsy procedure (for subgroup)
5. Non-smoker

For the young group:
1. Age 18-25 years
2. Male
3. No contra-indications for participation in strength training
4. No contra-indications for muscle biopsy procedure
5. Non-smoker

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Male

Target number of participants
60 older (45 in intervention group, 15 controls), 10 younger (intervention)

Total final enrolment
11

Key exclusion criteria
1. Unable to participate in the strength training program:
1.1. Severe back problems (eg acute hernia)
1.2. Problems with or prosthesis of the knee or hip
1.3. Unstable cardiovascular diseases
1.4. Neuromuscular disorders
2. Unable to provide a muscle biopsy (subgroup):
2.1. Coagulation problems
2.2. Taking blood thinners
3. Factors that might affect methylation status:
3.1. Regular participation in structured endurance and / or strength training in the last 12 months prior to the study
3.2. Smoking (must have stopped smoking for at least 30 years in order to participate)
3.3. Chronic diseases (e.g. type 2 diabetes, cancer)

Date of first enrolment
23/09/2016

Date of final enrolment
04/11/2016

Locations

Countries of recruitment
Belgium

Study participating centre
KU Leuven, Faculty of Movement and Rehabilitation Sciences
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Sponsor information

Organisation
Katholieke Universiteit Leuven (KU Leuven)

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Sponsor type
University/education

Website
https://gbiomed.kuleuven.be/english/research/50000737/groups/pash/research

ROR
https://ror.org/05f950310

Funder(s)

Funder type
Government

Funder Name
Fonds voor Wetenschappelijk Onderzoek [Research Foundation Flanders]

Results and Publications

Publication and dissemination plan
The researchers plan to publish the results of this study in several peer-reviewed papers.

Intention to publish date
01/03/2019

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Preprint results		02/07/2020	06/09/2021	No	No