Exercise-induced alterations in diurnal rates of muscle protein synthesis in young men

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From p12 of C1 protocol document:To assess how diurnal rates of muscle protein synthesis are altered during a short-term (3-day) implementation of resistance exercise training when compared to normal daily activity.

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

Summary

ID

NL-OMON42768

Source
ToetsingOnline

Brief title
Daily rates of protein synthesis during exercise

Condition

- Muscle disorders

Synonym
muscle growth, Muscle protein synthesis

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Heavy water, Muscle Protein Synthesis, Resistance Exercise

Outcome measures

Primary outcome

From p18 of C1 protocol document:

The main study endpoints are muscle protein synthesis (MPS) rates. In order to

determine the MPS, the following parameters will be measured:

* Muscle protein-bound L-[2,3,3,3-2H4]-alanine enrichment (expressed as MPE)

* Plasma free L-[2,3,3,3-2H4]-alanine enrichment (expressed as MPE)

* Saliva 2H2O enrichment (Expressed as APE)

Secondary outcome

From p18 of C1 protocol document:

Secondary endpoints include:

* Total plasma amino acids (AAmax [*mol/L])

* Plasma alanine concentrations (expressed as *mol/L)

Study description

Background summary

From p10 of C1 protocol document:

Skeletal muscle plays an important role as a metabolic organ and accounts for 30-45% of whole body protein metabolism. In addition, skeletal muscle plays a

central role in the regulation of whole body glucose regulation. Aging and disease, such as cancer or COPD, are associated with significant losses of muscle mass. Such losses of muscle mass is associated with poor physical performance and increases the likelihood of developing type II diabetes type, obesity and osteoporosis. Nutritional and/or physical activity interventions can influence skeletal muscle metabolism to achieve a more anabolic state, generally allowing for an increase or maintenance of muscle over a prolonged duration. Within skeletal muscle tissue, such an anabolic state is achieved when the on-going process of muscle protein synthesis occurs at a faster rate than the process of muscle protein breakdown. Thus, a key analytical target of research into the regulation of skeletal muscle mass is skeletal muscle protein synthesis, which is most credibly obtained by the use of stable isotope infusion techniques. Currently, the use of short-term (<9 hr) stable isotopically labelled amino acid tracer infusions are utilized to provide a mechanistic assessment of the shifts in rates of muscle protein synthesis that accompany certain phenotypic states (young vs. aged vs. disease) or various nutritional and physical activity interventions. However, the assessment of muscle protein synthesis using amino acid tracer infusions becomes much less reliable after a period longer than approximately 12 hrs and requires a high level of standardization in that test subjects must stay within the laboratory setting for the duration of the research protocol. While amino acid tracers can reliably assess acute interactions (e.g., single meal-based), such limitations in the amino acid tracer infusion method prevent scientific investigation into the impact of nutritional and physical activity interventions in the context real-life conditions carried out over an extended period of time (days-weeks).

Study objective

From p12 of C1 protocol document:

To assess how diurnal rates of muscle protein synthesis are altered during a short-term (3-day) implementation of resistance exercise training when compared to normal daily activity.

Study design

From p12-14 of C1 protocol document:

3.1 Screening

When volunteers respond to the advertisement, we will contact them by e-mail/phone and briefly explain the study. We will provide them with the information brochure and the informed consent (which they will bring during the screening). To assess whether volunteers are eligible to participate in this study, we will invite them to the University for screening at 08:30. Before we start the screening, we will explain the entire experimental trial and answer

any potential questions. We will then ask them to read, fill out, and sign the informed consent form. After signing the informed consent form, we will start the screening by going through the medical questionnaire to assess their general health, use of medication, and physical activity. Subsequently, we will assess body composition by performing a dual-energy X-ray absorptiometry (DEXA) scan and measure body height and body weight. DEXA is a simple and non-invasive procedure, which will take place at the University. Subjects will be instructed to lie down on a table and stay motionless for approximately 3 minutes during which the body scan takes place. Performing the above mentioned tests allow us to characterize the participants. In case of an unexpected medical finding, it is our duty to inform the subjects. If a participant does not want to receive this information, he cannot participate in this study.

Following the DEXA scan and anthropometric measurements, subjects will be familiarized and tested for strength on the exercise machines. Subjects will then be instructed on proper single legged weight-lifting technique on each exercise machine (leg-press and leg-extension) and complete a standardized testing protocol to determine a measurement of maximal strength (1RM) for each leg on each exercise machine. The testing protocol requires that the subjects complete sets on each exercise machine increasing in weight until volitional fatigue occurs, ideally occurring between 3-6 repetitions on the heaviest weight. The attained strength data will be compared to previously published data and used to calculate an estimation of 1RM. Following the determination of 1RM, subjects will be scheduled for their experimental testing days (dosing day, muscle biopsies, exercise sessions) before leaving for home.

3.2 Experimental trial

The experimental protocol consists of a 7-day testing period (Figure 1). Subjects will begin on day 1 by tracking normal dietary intake and daily activity using diary entries and will also being tracking steps taken with an *Actical* accelerometer which will be worn on the their wrist. On day 2, subjects will initiate the heavy water ingestion protocol, which will last for the remaining 6 days of the experiment. A detailed methodological description of the heavy water approach to measuring muscle protein synthesis is written in section 65.3.4. Subjects will report to the University at 0800 on the first day of the heavy water dosing protocol for the purpose of gathering baseline samples and supervising of the initiation of the heavy water (deuterium oxide) dosing protocol. This *dosing day* consists of the ingestion of 50ml of 70 APE enriched heavy water 8 times during waking hours, at: 0830, 0930, 1100, 1230, 1400, 1530, 1700, 1830 hr. Saliva and blood samples will be taken 4 times during the dosing day (0800 * basal, 1100, 1400, 1530) to track the rise in body water and plasma enrichment. After ingesting the 6th of 8 doses of heavy water, at approximately 1530 h, subjects will be free to go home where they will ingest the final 2 heavy water doses of the dosing day. For the remainder of the experiment, subjects will ingest one 50ml dose of 70 APE enriched heavy water each day upon waking to maintain 1-2 APE enrichment in body water (see

section 5.3.4). On day 4 of the experiment, subjects will report back to the University at 1100 to have a muscle biopsy taken from each leg, to have plasma and saliva samples taken and to complete the first unilateral resistance exercise session, beginning at 1200. Subjects will report to the University at 1200 on the following 2 days to have saliva and blood sampled and to complete the same unilateral exercise protocol. Subjects will complete, in total, 3 consecutive sessions of unilateral resistance exercise. Subjects will be provided with a drink containing 30g whey protein dissolved in 350ml water after each exercise training session and can go home afterwards. On the last experimental day (day 7), subjects will ingest their final dose of heavy water before coming into the University at 1100 to have their final saliva and blood samples collected as well as their final two biopsies. The experiment is finalized once the samples have been collected.

Intervention

From p17 of C1 protocol document:

To maximize muscle protein accretion, participants will perform a 3 day unilateral lower body resistance-type exercise training protocol under personal supervision. The training consists of a 5 min warm-up on a cycle ergometer and 4 sets on the leg-press and leg-extension machines (Technogym, Rotterdam, the Netherlands). The workload is set at 80% of the subjects* one-repetition maximum (8*10 repetitions) to stimulate muscle hypertrophy. Resting periods of 2 min are allowed between sets and 2 min between exercises.

Study burden and risks

The burden and risks associated with participation are minimal. Saliva sampling (9 samples) is risk-free. Blood sampling is minimal (9 x 10mL total) and will be conducted using catheter placement during the dosing day (4 blood samples) and with the single venipuncture method on each of the following 5 days (1 sample per day). Muscle biopsies will be taken under local anesthesia by an experienced physician, but may cause some minor discomfort up to 24 h after completion. The discomfort is comparable to muscle soreness or the pain one has after bumping into a table. Participants will come to the University for seven visits: 1 screening visit (1.5 hours), 1 dosing day (day 2 - ~9 hours) and 5 times (1 hour each) for tissue sampling (blood, saliva, muscle) and/or the exercise sessions. During the screening visit, we will perform a DEXA scan and determine maximal strength (1RM) on each exercise machine. Furthermore, we will ask the participants to fill out a medical questionnaire. For the duration of the study protocol, subjects will ingest doses of 50ml of 70% deuterium oxide ($2H_2O$) to enrich the body water pool to approximately 1 APE (atom percent excess, similar to percent). Deuterium oxide dosing to achieve a body water enrichment of 1 APE is completely safe as it is far below the threshold for biological toxicity in humans (approximately 20 APE) and will be returned to

baseline enrichments within 30 days.
Deuterium oxide intake in small amounts increases the presence of deuterium on H2O molecules in the body water pool of the test subject. The deuterium is available for transfer from the D2O molecule for incorporation into any endogenously synthesized substrate utilizing H2O as reagent in the biochemical reaction. For the aims of this study, the endogenously synthesized amino acid alanine is of primary analytical interest. Once a deuterium atom has been incorporated into newly formed alanine, the amount of alanine incorporated into proteins can be accurately measured. There are no adverse health effects associated with deuterium oxide dosing within the ranges of the present study. However, a small fraction of the studies using heavy water in humans have suggested that short-term vertigo (similar to dizziness) may occur in some subjects during the initial phases of heavy water dosing if the doses are taken too rapidly. The study in which the current dosing protocol was based off of reported that only one subject experienced any form of dizziness, which subsided within 30 minutes. We will be monitoring subjects during the initial dosing phase in the current study in case any such dizziness occurs and do not expect any complications.

Subjects will be required to fill in activity and dietary records on each day of the protocol and one day prior (7 days total). Furthermore, subjects will wear accelerometer watches for the purpose of quantitatively tracking physical activity levels throughout the day. There is no direct benefit for the participants except for their contribution to the scientific knowledge of exercise and nutritional strategies to improve muscle mass, which will be obtained from this study and used in the future.

Contacts

Public
Universiteit Maastricht

Universiteitsingel 50
Maastricht 6229 ER
NL
Scientific
Universiteit Maastricht

Universiteitsingel 50
Maastricht 6229 ER
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Healthy males
* Age between 18 and 35 y
* BMI between 18.5 and 30 kg/m2
* Moderate level of physical activity (exercising 2-4 hours per week)

Exclusion criteria

* Celiac disease
* Lactose intolerance
* Smoking
* Diabetes
* Cancer
* Cardiovascular Disease
* Donated blood within the last 3 months
* Diagnosed GI tract diseases
* Arthritic conditions
* A history of neuromuscular problems
* Any medications known to affect protein metabolism (i.e. corticosteroids, non-steroidal anti-inflammatories, or prescription strength acne medications).

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-09-2015
Enrollment:	17
Type:	Actual

Ethics review

Approved WMO

Date:	14-08-2015
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 20277
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL52517.068.15
OMON	NL-OMON20277

Study results

Date completed: 01-04-2016

Actual enrolment: 12

Summary results

Trial is onging in other countries