Skeletal muscle structure and function in relation to post-exertional malaise in patients with PASC and ME/CFS

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To obtain insight whether skeletal muscle adaptations can explain post-exertional fatigue malaise in patients with PASC and ME/CFS, the present study will address the following objectives: Primary objectives:• To determine markers for skeletal…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Viral infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON56099

Source
ToetsingOnline

Brief title
STOP PASC-ME/CFS

Condition

- Viral infectious disorders

Synonym
PASC en ME/CFS

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Inflammation, Long-COVID, ME/CFS, Skeletal muscle

Outcome measures

Primary outcome

The study parameters are listed below. A detailed description of the methodology to determine these parameters is written in the section on data and statistical analysis (section 10). The primary outcome parameters are skeletal muscle and blood determinants (see 5.1.1). Secondary outcome parameters include exercise tolerance, maximal and submaximal parameters of aerobic function (i.e. VO2max and lactate threshold), intracellular metabolite concentrations derived from biopsies, heart rate variability and measures of muscle oxygenation derived via near-infrared spectroscopy (NIRS).

4.6 Main study parameter/endpoint

Primary outcome parameters of this study are markers for local and systemic inflammation, mitochondrial respiratory function and myokine concentrations. Each of these variables will be assessed via muscle biopsy of the vastus lateralis muscle and venous blood samples.

The following primary parameters will be evaluated:

Markers of local (muscle) and systemic (venous blood) inflammation:

• macrophage count and infiltration into skeletal muscle

• IL-6, creatine kinase, troponin

Mitochondrial function:

• markers for OXPHOS subunits, mitochondrial fission/fusion and mitophagy

• Mitochondrial ROS production

• Electron microscopy: mitochondrial ultrastructure, intramuscular glycogen deposits and lipid storage

Myokine concentrations:

• IL-6, GDF15, FGF-21, and other newly discovered myokines

Secondary outcome

Secondary outcome parameters of this study involve other parameters of exercise tolerance and aerobic function. The peak work rate attained during ramp incremental exercise (WRpeak) will be used to measure exercise tolerance. The key parameters of aerobic function that will be assessed include: VO2max, the gas exchange threshold, the respiratory compensation point, the gain (i.e. efficiency) of the oxygen uptake (VO2) response to ramp incremental exercise, and the mean response time of the VO2 response.

Other secondary outcome measures include the non-invasive measurements of muscle oxidative metabolism (i.e. tissue saturation index [TSI], oxygenated hemoglobin [O2Hb] and deoxygenated hemoglobin [HHb], measured by NIRS) during ramp incremental exercise, the heart rate variability (HRV), and daily activity. Relationships between these parameters and the parameters of exercise tolerance, aerobic function, muscle biopsy, proteomics, metabolomics, transcriptomics and auto-immunity will also be explored.

Measured through heart rate monitoring during 14 consecutive days, to establish the total time spent in low, moderate and vigorous intensity activities.

Activity monitors will be used to determine the total step count during the 14

day period and subjects will also be asked to keep an activity diary.

Study description

Background summary

Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) are severely debilitating diseases mainly characterized by chronic fatigue, post-exertional malaise (PEM) and cognitive impairment with autonomic, neuro-endocrine, immunological and cognitive involvement1-3. Particularly, skeletal muscle-related complaints, such as extreme fatigue, muscle weakness and muscle pain, are symptoms that tremendously decrease the patients quality of life, The key symptom, PEM, distinguishes PASC and ME/CFS from other more common fatigue conditions and is characterized by worsening or relapse of symptoms (including sleep dysfunction, cognitive impairment and extreme skeletal muscle fatigue) after physical activity, which can last for days or weeks1,3,4. We recently reviewed the skeletal muscle alterations in both acute SARS-CoV-2 infection and patients with Long COVID, and concluded that post-exertional malaise in patients with Long COVID cannot be explained by current knowledge on skeletal muscle structure and function1.

A possible lead to the understanding of PEM in Long COVID and ME/CFS pathophysiology is provided by the observation that most cases appear to have an infectious onset5-7. Following SARS-CoV-2 infection, 10-30% of patients exhibit post-infectious fatigue syndrome, called Long COVID or post-COVID condition8. PEM is the hallmark symptom of Long COVID and ME/CFS and a criterion for CCC, ICCC and IOM case definitions. Little is known about the underlying pathophysiology of skeletal muscle abnormalities, including PEM. No treatment options are available, apart from the advice to patients to avoid exercise or exercise below an (unknown) threshold.

Due to the heterogeneity of patients, these muscle-related symptoms may vary dramatically, and is likely multifactorial in nature. Whilst long-term consequences of hospitalization are known, the widespread incidence of muscle-related symptoms suggests that skeletal muscle adaptations seen in non-hospitalized patients with PASC and ME/CFS stand apart from those seen in critical illness myopathy.

The muscle weakness can range from mild to severe, and such symptoms may persist long after the viral infection has resolved. The high prevalence of skeletal muscle-related symptoms hint towards structural and functional alterations in skeletal muscle in patients with PASC and ME/CFS9-11. In this study, we aim to study alterations in intracellular skeletal muscle structure

and function and the immune response that will help to explain why patients with PASC and ME/CFS suffer from post-exertional fatigue.

Study objective

To obtain insight whether skeletal muscle adaptations can explain post-exertional fatigue malaise in patients with PASC and ME/CFS, the present study will address the following objectives:

Primary objectives:
• To determine markers for skeletal muscle structure and function (such as mitochondrial ultrastructure and function, viral infiltration, metabolite concentrations, myokine secretion), the immune response and circulating myokines (muscle-derived molecules), in non-hospitalized patients with PASC, ME/CFS and healthy controls.

Secondary objectives:
• To determine each of the above variables both before and after induction of post-exertional malaise, and assess the relationships between the measures obtained from muscle biopsies and parameters of exercise tolerance.

Study design

Case-control study with assessments before and after an induction of post-exertional malaise. 26 PASC patients, 26 ME/CFS patients and 30 matched healthy controls who have recovered from a SARS-COV-2 infection will be recruited for the study. Participants are required to visit the laboratory for a total of 5 experimental sessions, for a total duration of approximately 8 hours. Four measurements will take place within a time window of 2 weeks. On day 10, patients will fill in a digital questionnaire. The last time point will be 1 year after the start of the study. See Figure 1 for an overview of study design.

26 participants with PASC and 20 patients with ME/CFS (equal split between sexes) between the ages of 18-65 yrs will be recruited for the study. 30 healthy participants matched for age BMI and preferably physical activity levels will be included as a control group

Participants will be required to visit the laboratory on 4 separate occasions over a 2 week period immediately prior to and following a maximal exercise test. One year (± three months) we will require one additional visit. After the first visit, participants will be asked to confirm dates for the subsequent visits over the next 2 weeks face-to-face in the laboratory. Participants will be instructed not to consume alcohol or perform strenuous exercise within the 24 h preceding each exercise test, and to abstain from caffeine consumption for at least 3 h.

Study burden and risks

A muscle biopsy is an invasive procedure, however, the procedure is relatively simple and poses little risk to the participants (Derry et al., 2009; Edwards et al., 1983). For one, there is an extremely low risk of an allergic reaction to the local anesthetic injection. During the needle biopsy (which takes about 5 seconds) participants may experience mild discomfort, such as a sensation of pressure. The discomfort or experienced muscle stiffness after the needle biopsy should resolve in one or two days after the procedure and is usually well controlled with pain relievers. There is a very low risk of internal bleeding at the biopsy site, which can result in more prolonged pain and stiffness in the leg. However, subjects routinely start exercising at normal capacity within one-to-two days after the biopsy. Local bruising and fainting can occur, although these events occur infrequently. Although there is a very rare risk (< 0.5%) of damage to a muscle tissue or a small nerve branch, which could result in partial weakness of the m. vastus lateralis, this would likely have no impact on daily activities. Nerve injuries usually resolve in 8-12 months, but there is a theoretical risk of mild leg weakness. Furthermore, there can be a risk of wound infection with the procedure, although this risk is minimal since needle biopsies are taken under sterile conditions. In most cases the muscle biopsy will result only in a small scar, which usually disappears within 12 months. To allow proper healing of the incision and minimize any risk of infection, subjects should avoid prolonged submersion in water for 4 days after the biopsy. Also, repeat biopsies are well tolerated and therefore allow follow-up studies after an intervention (Edwards et al., 1983). In addition, muscle needle biopsies do not entail detrimental effects or additional risks on subsequent physical performance as has been shown by earlier research (Altenburg et al., 2007; Babcock et al., 2012; Stathis et al., 1994; Withers et al., 1991).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject with PASC must meet all of the following criteria:
* Non-hospitalized individuals with prior confirmed diagnosis of severe acute respiratory coronavirus 2 (SARS-CoV-2) infection by reverse transcription-polymerase chain reaction testing or serology (wantai) testing
* Individuals with diagnosed PASC by a post-covid physician
* >3 months of symptoms
* Post exertional malaise, according to the DSQ-PEM questionnaire or 1:1 interview with post-covid physician
* No symptoms present before confirmed diagnosis of severe acute respiratory coronavirus 2
* Aged between 18-65 years

In order to be eligible to participate in this study, a subject with ME/CFS must meet all of the following criteria:
* Fulfill the Canadian Consensus Criteria (CCC)
* Post exertional malaise, according to the DSQ-PEM questionnaire or 1:1 interview with post-covid physician
* >3 months of symptoms
* ME/CFS diagnosis <10 years ago
* Aged between 18-65 years
* Confirmed diagnosis of severe acute respiratory coronavirus2 (SARS-CoV-2) infection by reverse transcription-polymerase chain reaction testing or serology (wantai) testing

For the healthy controls:
* Aged between 18-65 years
* Confirmed diagnosis of severe acute respiratory coronavirus2 (SARS-CoV-2)

infection by reverse transcription-polymerase chain reaction testing or serology (wantai) testing without admission

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

* History of asthma, stroke, chronic obstructive pulmonary disease, congestive heart failure, heart surgery, or congenital heart diseases
* Severe illness (e.g., cancer, CHD, uncontrolled diabetes)
* Current treatment with drugs known to interfere with metabolism e.g. systemic corticosteroids, statins, SGLT2 inhibitors, GLP1 receptor agonists or immune modulatory drugs in the last three months.
* Severe psychiatric or mood disorders
* Are current smokers or have been a regular smoker within the last 12 months
* Insulin pump therapy
* Symptomatic autonomic or distal neuropathy
* BMI >35 due to adiposity, since this is known to cause difficulties in obtaining muscle biopsies.
* Pregnancy
* Recent acute myocardial infarction (<6 months)
* Uncontrolled arrhythmia/severe conduction disorder (atrial fibrillation or second/third degree AV block) causing hemodynamic compromise
* Implantable pacemaker or other cardiac device with complete ventricular pacing
* Uncontrolled heart failure with hemodynamic compromise
* Uncontrolled hypertension (Systolic Blood Pressure >150 mmHg and Diastolic Blood Pressure > 100 mmHg on repeated measurements)
* Active infection, anaemia, severe renal dysfunction (estimated Glomerular filtration rate <30 ml/min/1,73m2) likely to significantly impact on exercise performance
* > 6 alcohol units per day or >14 alcohol units per week
* Use of anticoagulants or anti platelet therapy

Study design

Design

Study type:	Observational invasive
Intervention model:	Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-01-2022
Enrollment:	82
Type:	Actual

Ethics review

Approved WMO Date:	20-10-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-02-2023
Application type:	Amendment
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Approved WMO Date:	09-11-2023
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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	NL78394.018.21