Plan Overview

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Title: Part 1: A longitudinal approach to characterize loss of muscle mass and function in aging humans – the importance of peripheral nerve integrity

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Project abstract:

The loss of muscle mass and function (i.e sarcopenia) engenders numerous aspects of life and health. It is a health hazard recognized by WHO, and due to demographic changes, sarcopenia is associated with very large and increasing societal costs and individual suffering. Most of our knowledge regarding the muscle deconditioning processes stem from animal models. Attempts to confirm or dispute these findings have been done in humans. However, human studies have for simplicity mainly been conducted with a cross-sectional design. This design compares age-cohorts raised under different conditions and does not take into account the individual variation in factors with huge impact on sarcopenia, such as genetic make-up, physical activity and medical history. This proposal is based upon a longitudinal cohort comprised of a representative sample of healthy women of men, with a follow-up almost 50 years after the first exploration, and with four data collection time points with objectively measured outcomes. It is a unique cohort since monitoring of started in late puberty and the participants are now at an age where subclinical sarcopenia will emerge. The participants represent those that will be major consumers of health- and social care in the next coming 25 years. The current design will enable us to establish the biological variability in adult life-time changes of muscle function and mass, and to shed light on the mechanisms underpinning the biological variability. This model allows us to evaluate the role of lifestyle and physical activity on muscle health throughout life. Broadly, factors driving the sarcopenic process can be categorized as being primarily of neurogenic origin (denervation, axon impairments and changes to the functionality of terminal Schwann cells) or primarily myogenic origin (disturbances in metabolic-anabolic-catabolic processes, dysfunctional or exhausted

dynamics in cell accretion, accumulation of somatic mutations and inflammation). The interaction between myogenic and neurogenic sarcopenic factors affect a number of molecules involved in the depolarizing and bilateral non-depolarizing communication across the neuromuscular junction (NMJ) interface, which will trigger a number of well-established secondary manifestations in the target myofiber. As the sarcopenic process progresses, myogenic factors become increasingly important and also new elements are added to the equation, such as endocrinescence and changes to the extracellular matrix (the myo-loge scaffold). The effects added by all factors involved will probably set the pace and extent of muscle deconditioning, making the muscle more vulnerable and generating a vicious circle leading inexorably to a worsening of the sarcopenic prognosis. Yet, increased physical activity can partly attenuate the muscle deconditioning processes and has been shown to preserve the integrity of the NMJ in animal models. Using an unparallel longitudinal human cohort, this study will explore with emphasis on the early phase of sarcopenia to reveal factors that are likely to be driving at least at the onset (triggers) of the sarcopenic process. We will conduct analyses of neurogenic components by by EnEEG, skin biopsies and needle EMG, muscle gross anatomy by MRI, and muscle tissue structure employing biopsies. Molecular factors with a role in the establishment and maintenance of the NMJ and skeletal muscle remodeling capacity in response to disturbed innervation will be investigated, in particular. A machinery of paramount importance in all cellular adaptive processes is the ubiquitin proteasome system (UPS) since it regulates action/dwell-time of proteins intracellularly. Based on the precise information originating from all these analyses, we will use in vitro approaches to validate and challenge identified candidate mechanisms. The over-riding hypothesis is that the integrity and function of MU differ between subjects as we age. We also propose that NMJ disintegration/denervation vs. maintained integrity/successful re-innervation are reflected in measureable variables in the skeletal muscle that can be assessed clinically in humans. We hypothesis further that a high level of MU remodeling may translate into more well-preserved function and prolonged era of subclinical sarcopenia; while low levels of MU remodeling may indicate early loss of muscle function and mass. The specific aims are: Aim 1: Phenotype: To associate measurements of integrity of peripheral innervation (nerve and MU), to muscle morphology and muscle molecular adaptive processes and its predictive ability for future loss of power and mass (at 65y) Aim 2: Prediction: Identify clinical and molecular factors measurable in adolescence and young adulthood that are predictive for integrity of peripheral innervation (nerve and MU) at early aging Aim 3: Proteolysis: Characterize skeletal muscle enriched members of the Ubiquitin-proteasome system over the life-course and their relation to skeletal muscle remodeling, mass and function as well as to NMJ remodeling in early aging. Aims 1-3 will create a platform for future studies in this patient cohort

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Part 1: A longitudinal approach to characterize loss of muscle mass and function in aging humans – the importance of peripheral nerve integrity

General Information

Project Title

A longitudinal approach to characterize loss of muscle mass and function in aging humans – the importance of peripheral nerve integrity

Project Leader

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Registration number at the Swedish Research Council

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1

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Description of data – reuse of existing data and/or production of new data

How will data be collected, created or reused?

Data collection will be performed in 2020/2021 at age 62 and at age 65 2023/2024 of the human longitudinal cohort study SPAF-1958. At baseline, in 1974, six geographic areas in Sweden were systematically selected based on reflecting climate and population density representative of Sweden as a whole. In each area, one upper secondary school was randomly selected, from which 429 (224 male, and 205 female) pupils in the lowest grade level were randomly selected to be included in the study. The entire cohort was invited for questionnaire and testing at age 16, 34 and 52. The blood samples that were collected at age 52 are available for further analyses. A smaller group (n=83) contributed with muscle biopsies at age 16 and 27. In the current project a third extended follow-up is planned almost 50 years after the first baseline measurements, when the participants are 62 years of age. At baseline, consent to a muscle biopsy and extra testing was given by 116 of the participants (69 boys and 47 girls). Eleven years later, at the age of 27, this subgroup was invited to a follow-up and a total of 83 participants (72%) (55 men and 28 women) consented to take a new muscle biopsy also at the age of 27. Biopsy materials from both age 16 and 27 are still available. Importantly, no differences have been identified between the biopsy subgroup and the remaining members of the cohort with respect to body dimensions, blood pressure, resting heart rate or most of the measures of physical capacity at 16, 34 or 52 years of age.

Three hundred and eighty-one participants from the baseline cohort (90%) have been identified (i.e. being alive and with a known address and personal identity number). All subjects will be contacted during spring-summer 2020 and asked to participate in some or all of: [1] questionnaire, [2] testing of physical performance and general health, and [3] extended testing of muscle function and structure. Testing of physical performance and health, and questionnaire completion will take approximately 4 hours. The extended testing of muscle function and structure will take ~4 hour. All individuals will be asked to reply to the questionnaire and to participate in functional and neurological testing. Based on previous participation-rate we assume 80% (n~310) [1] will participate in questionnaire, and 50% (n~190) [2] in functional and neurological testing including EnEEG. All individuals that gave skeletal muscle

biopsy at age 27y and those with signs of neuropathy at 62y will be asked to give a new biopsy for skeletal muscle characterization, a skin biopsy for evaluation of small fibre neuropathy and execute and EMG-test to define MU number and size. We assume 10-15% (n~50-60) will be included in this part of the project [3]. At age 65y those who participated at stage [3] will be asked to perform [1-3] again and the other participants (no earlier biopsies and no signs of neuropathy at age 62y) will be asked to reply on the questionnaire perform the functional and neurological tests again [1-2]. Those who have developed signs of neuropathy at age 65 will be added to the group with an extended test battery (EMG, MRI, tissue biopsies).

What types of data will be created and/or collected, in terms of data format and amount/volume of data?

Enkätsvar som samtliga deltagare. Uppskattat antal deltagare är 200 för blodprov och max 100 för biopsier Blod: ca 50 ml per deltagare per uppföljning Hudbiopsier: 1-3 biopsier per deltagare per uppföljning Muskelbiopsier: 1 per deltagare per uppföljning

Documentation and data quality

How will the material be documented and described, with associated metadata relating to structure, standards and format for descriptions of the content, collection method, etc.?

Samtliga deltagare har sedan tidigare testning redan ett kodnummer. Under datainsamlingen kommer personens namn kontrolleras mot hens kodnummer vid respektive undersökning för att insamlade uppgifter ska registreras på rätt person. Kodlista med namn är tillgänglig för forskningsledarna under hela datainsamlingen för att kunna matcha rätt person med rätt kodnummer vid testningen. När alla insamlade uppgifter samlas i databas och statistikprogram anges endast kodnummer och kön. Kodnyckeln förvaras i låst utrymme i forskargruppen. Primärdata lagras i ELN samt för fysiska kopior i KI:s arkiv i minst 30 år. Kodnyckeln kommer sparas eftersom detta är en longitudinell studie med ytterligare planerade
datainsamlingar.
Enkäter skickas ut via post eller digitalt. Svaren i de insamlade enkäterna matas in i digitalt format. Datainsamlingen sker genom att fp kommer till undersökningslokalen och deltar i tester under en-två dagar.

Blodproverna skickas för analys samt sparas i -80grader i biobank.Muskelbiopsierna snittas för analys av muskelfibertyp samt innervering och övrig morfologi. Prover fryses i flytande kväve/för-kyld isopentan och förvaras vid -80°C tills analys utförs. Samtliga prover förvaras i befintlig biobank vid Karolinska Universitetssjukhuset. Muskelsnitt analyseras exv. för fiberstorlek och fiberklustring, innervering, cellkärnor, satellitceller, kapillärisering enligt standardmetoder på vårt laboratorium. Muskelvävnad bearbetas för analys av genutryck, metabolism och olika aspekter av proteinhantering enligt sedvanliga metoder på vårt laboratorium. Nervfibertäthet: Biopsimaterialet fixeras i fixeringsmedel mellan 18–24 timmar. Därefter skickas hudvävnaden kyld till neuropatologen för immunohistokemisk hantering inkl. snittning och färgning. Immunohistokemisk analys av hudbiopsierna genomförs där nervfibrer färgas med efterföljande kvantifiering av nervfibertätheten (nervfibrer per mm hud); resultatet kan jämföras med publicerade normalmaterial samt lokal referensdatabas. Resultatet sparas och resterande vävnadsmaterial sparas för framtida forskning i biobank.

How will data quality be safeguarded and documented (for example repeated measurements, validation of data input, etc.)?

Varje deltagare har ett kodnummer. Vid resultatbearbetning anges kodnumret och initialerna för varjedeltagare. Alla uppgifter matas in i en databas, som REDCap som är ett system via Karolinska insitutet. All laboratoriearbete dokumenteras fortlöpande i ELN som signeras av ansvariga forskare. Alla undersökningar utförs enligt faställda SOPs av ansvarig och för metoden med kompetens.

Storage and backup

How is storage and backup of data and metadata safeguarded during the research process?

Alla uppgifter matas in i en databas som REDCap, ett system via Karolinska insitutet. All datainsamling dokumenteras och arkiveras i ELN eller andra av KI godkända platser för arkivering.

How is data security and controlled access to data safeguarded, in relation to the handling of sensitive data and personal data, for example?

Se ovan

Legal and ethical aspects

How is data handling according to legal requirements safeguarded, e.g. in terms of handling of personal data, confidentiality and intellectual property rights?

Samtliga deltagare har sedan tidigare testning redan ett kodnummer. Under datainsamlingen kommer personens namn kontrolleras mot hens kodnummer vid respektive undersökning för att insamlade uppgifter ska registreras på rätt person. Kodlista med namn är tillgänglig för forskningsledarna under hela datainsamlingen för att kunna matcha rätt person med rätt kodnummer vid testningen. När alla insamlade uppgifter samlas i databas och statistikprogram anges endast kodnummer och kön. Kodnyckeln förvaras i låst utrymme i forskargruppen. Primärdata lagras i ELN samt för fysiska kopior i KI:s arkiv i minst 30 år. Kodnyckeln kommer sparas eftersom detta är en longitudinell studie med ytterligare planerade
datainsamlingar.

How is correct data handling according to ethical aspects safeguarded?

Godkänd enligt GDPR samt samtycke inhämtad från samtliga som valt att ingå i studien. Dokumenterd process (enligt ovan) om hur datathantering, process samt lagring ska ske och i enlighet med gällande förordning

Accessibility and long-term storage

How, when and where will research data or information about data (metadata) be made accessible? Are there any conditions, embargoes and limitations on the access to and reuse of data to be considered?

Alla data kommer göras tillgängliga (i anonymiserad form) i samband med i samband med publisering i enlighet med creative commons framework

In what way is long-term storage safeguarded, and by whom? How will the selection of data for long-term storage be made?

All datainsamling dokumenteras och arkiveras i enlighet med KI regelverk. Primärdata lagras i ELN samt för fysiska kopior i KI:s arkiv i minst 30 år. Kodnyckeln kommer sparas eftersom detta är en longitudinell studie med ytterligare planerade datainsamlingar.

Will specific systems, software, source code or other types of services be necessary in order to understand, partake of or use/analyse data in the long term?

Databas REDCap, ett system via Karolinska insitutet. All datainsamling dokumenteras och arkiveras i ELN eller andra av KI godkända platser för arkivering.

How will the use of unique and persistent identifiers, such as a Digital Object Identifier (DOI), be safeguarded?

Samtliga deltagare har sedan tidigare testning redan ett kodnummer. Under datainsamlingen kommer personens namn kontrolleras mot hens kodnummer vid respektive undersökning för att insamlade uppgifter ska registreras på rätt person. Kodlista med namn är tillgänglig för forskningsledarna under hela datainsamlingen för att kunna matcha rätt person med rätt kodnummer vid testningen. När alla insamlade uppgifter samlas i databas och statistikprogram anges endast kodnummer och kön. Kodnyckeln förvaras i låst utrymme i forskargruppen

Responsibility and resources

Who is responsible for data management and (possibly) supports the work with this while the research project is in progress? Who is responsible for data management, ongoing management and long-term storage after the research project has ended?

Maria Westerståhl is responsible for data management during the progress of the study as well as after the research project has ended

What resources (costs, labour input or other) will be required for data management (including storage, back-up, provision of access and processing for long-term storage)? What resources will be needed to ensure that data fulfil the FAIR principles?

The cots will be covered by the division - during the study by the grant from Sweedish research council and after the study by the government founding