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

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Creators: Thomas Gustafsson, Maria Surname, Brun Ulfhake

Affiliation: Karolinska Institutet

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ORCID iD: 0000-0002-1559-4206

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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 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

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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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General Information

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Thomas Gustafsson
Brun Ulfhake
Maria Westerståhl

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

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).

Documentation and data quality

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 datainsamlings.

Enkäter skickas ut via post eller digitalt. Svaren i de insamlade enkätarna matas in i digitalt format. Datainsamlingen sker genom att fp kommer till undersökningslokalen och deltar i tester under en-två dagar.


Varje deltagare har ett kodnummer. Vid resultatbearbetning anges kodnumret och initialerna för varje deltagare. Alla uppgifter matas in i en databas, som REDCap som är ett system via Karolinska institutet. All laboratoriearbete dokumenteras fortfarande i ELN som signeras av ansvariga forskare. Alla undersökningsutförs enligt fastställda SOPs av ansvarig med kompetens.

Storage and backup

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

Se ovan

Legal and ethical aspects


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

Accessibility and long-term storage

Alla data kommer göras tillgängliga (i anonymiserad form) i samband med i samband med publicering i enlighet med creative commons framework. All datainsamling dokumenteras och arkiveras i enlighet med KI regelverk. Primärdataläggas 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 datainsamlings.

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

**Responsibility and resources**

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

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