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the Hospital-ADL study

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SYMPOSIUM ABSTRACTS

SYMPOSIUM 1 – EXERCISE AND NUTRITION TO COMBAT SARCOPENIA

Synthesising skeletal muscle with resistance exercise: one protein at a time

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Human skeletal muscle is a highly malleable tissue that can alter its phenotype in response to repeated bouts of contractile activity (i.e. exercise) and altered nutrient availability, particularly protein. The net balance between the continuous and simultaneous processes of muscle protein synthesis (MPS) and muscle protein breakdown (MPB) determines whether skeletal muscle tissue is increasing (hypertrophy) or decreasing (atrophy) total protein content, which is a key regulator of overall skeletal muscle mass. Muscle hypertrophy can only occur when there is an accumulation of muscle proteins during repeated periods of anabolism, such as that induced by performance of resistance exercise and protein ingestion, that exceeds the loss of muscle proteins during intervening periods of catabolism. When assessing muscle protein synthesis, commonly utilised acute measurements of protein synthesis using labelled amino acid tracers are limited by the timing of the assessment. In particular, the brief duration of tracer administration in a laboratory setting under sterile conditions fails to integrate all aspects of habitual ('free-living') behaviour such as sleeping, feeding, and/or other physical activity and physiological stresses. The use of longer-term labelling using deuterium oxide (D_2O) provides an alternative method to investigating rates of muscle protein synthesis and breakdown as it can be administered via drinking water and under real-world conditions. This presentation focuses on the evolving use of D_2O as a metabolic tracer to measure both fractional and individual rates of muscle protein synthesis following resistance exercise to provide novel mechanistic insight to changes in the muscle proteome with advancing age.

The importance of physical activity for maintaining mitochondrial function across healthspan

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Mitochondrial content and function decline during ageing, leading to alterations in glucose and lipid utilisation, reduced insulin sensitivity, increased adiposity and loss of functional ability. Thus, strategies aimed at maintaining or boosting mitochondrial function hold tremendous therapeutic potential for mitigating chronic diseases of ageing. The best countermeasure currently identified to increase mitochondrial content in skeletal muscle is exercise; however how this adaptation occurs at the cellular level is poorly understood. Research has identified that exercise transiently activates a number of cellular stress responses that initiate mitochondrial remodeling, providing therapeutic and ergogenic targets to explore. This talk will highlight exercise approaches to manipulate mitochondrial function in skeletal muscle and discuss the therapeutic implications of these strategies for healthy ageing.

Nutritional approaches to combat sarcopenia

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The exact mechanisms that lead to sarcopenia are still unknown. However, evidence supports the concept that resistance to feeding induced stimuli is one of the key causes. More specifically, old muscle is less able than young muscle at increasing the synthesis of new proteins after a feeding stimulus. This metabolic defect, termed anabolic resistance, results in a net loss of muscle protein and subsequently a loss of muscle mass. If sarcopenia's origin is partly related to nutrition responses is there a nutritional solution? This talk will explore the potential mechanisms of sarcopenia in addition to addressing some of the potential nutrient-related solutions including protein nutrition and fish oil.

SYMPOSIUM 2 – THE OPERATIONAL DEFINITION OF SARCOPENIA: DO WE NEED TO ESTABLISH A CONSENSUS IN AUSTRALIAN AND NEW ZEALAND (AGAIN)?

Sarcopenia definitions: rationale, processes and limitations

M Sim
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The ANZSSFR Task Force on Diagnostic Criteria for Sarcopenia recommended the use of the original European Working Group on Sarcopenia in Older People (EWGSOP) operational definition of sarcopenia in 2018. EWGSOP recommended sarcopenia be defined by the presence of low muscle mass in conjunction with weak muscle strength and/or poor physical function. In January 2019, EWGSOP published revised guidelines (EWGSOP2) for the definition and treatment of sarcopenia. EWGSOP2 defines sarcopenia using low muscle strength as the primary parameter, with diagnosis confirmed by the presence of low muscle quantity or quality. Physical performance measures now only categorise the severity of sarcopenia in EWGSOP2. A key aim of EWGSOP2 was to provide clear cut-points for these measurements in order to increase harmonisation of sarcopenia studies and clinical utility. However, the methods by which EWGSOP2 have derived these cut-points are problematic, with numerous inconsistencies highlighted by researchers since its publication. In March 2019, recommendations from the Sarcopenia Definition and Outcomes Consortium Conference (SDOC; an extension of the 2014 US FNIH Sarcopenia Project) were released. Preliminary findings suggest grip strength is an important discriminator of mobility disability (walking speed <0.8 m/s) and other adverse outcomes (e.g. falls), while lean mass, measured by dual-energy X-ray absorptiometry, is a poor discriminator of mobility disability. Notably, EWGSOP2 cut-points are generally based on estimates of -2 standard deviations below mean reference population values from previous analyses (without any specific sarcopenia outcome), whereas SDOC is adopting new classification and regression tree analyses with mobility disability as the outcome. This presentation will discuss the rationale and processes for the development of current sarcopenia definitions, while also covering their potential limitations. In light of multiple current sarcopenia definitions, initiatives are clearly required to reduce ambiguity among researchers and health care professionals on appropriate methods for the diagnosis of sarcopenia.

The ANZSSFR task force on diagnostic criteria for sarcopenia: initial process and outcomes, and future possibilities

J Zanker
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The ANZSSFR Task Force on Diagnostic Criteria for Sarcopenia was established in 2017 to adopt and promote an operational definition of sarcopenia for use by clinicians and researchers in Australia and New Zealand. The Task Force was initiated due to the absence of international consensus regarding the diagnostic criteria for sarcopenia, and the recognition that there was a lack of understanding about sarcopenia amongst clinicians, researchers and members of the public in Australia and New Zealand. The Task Force adopted a modified Delphi method to achieve consensus. The Delphi method is an iterative process of consultation and exploration of disagreement amongst participants. The Task Force, comprised of 24 clinicians and researchers with an interest in sarcopenia, achieved consensus with 94% of members supporting adoption and promotion of the European Working Group on Sarcopenia in Older People (EWGSOP) definition, and the need for future validation of existing cut-points developed from international cohorts using Australian and New Zealand data. However, the EWGSOP subsequently released a revised sarcopenia definition, and an additional definition from the Sarcopenia Diagnostic and Outcomes Consortium (SDOC) is in preparation. These new definitions are likely to increase confusion for Australian and New Zealand clinicians and researchers with an interest in sarcopenia, highlighting the need for a clear and consistent message regarding the preferred operational definition. A modified Delphi consensus may be a path towards improving both the understanding of sarcopenia and the credibility of the field in the eyes of the wider community. To ensure representation by all stakeholders and to best promote the consensus outcomes, widespread participation should be sought. A diverse participation group could include researchers, clinicians, policy makers, members of the public and those living with sarcopenia. This presentation will summarise potential methods for expanding the original ANZSSFR Task Force on Diagnostic Criteria for Sarcopenia.

Interactive discussion: what is needed to establish a consensus operational definition of sarcopenia in Australia and New Zealand

D Scott
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Consensus definitions of sarcopenia with a focus on clinical relevance were published almost a decade ago, and the provision of a code for sarcopenia in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10-CM) in 2016 was another step towards increasing clinical recognition of sarcopenia. Despite these achievements, there is little evidence that assessment and treatment of sarcopenia are systematically performed by clinicians in Australia and New Zealand, and public awareness of sarcopenia appears exceedingly low. The ANZSSFR Task Force on Diagnostic Criteria for Sarcopenia was formed in 2017 to address poor awareness and knowledge of sarcopenia, and particularly, to establish a consensus on an operational definition of sarcopenia in Australia and New Zealand. The Task Force published the findings of its first expert-led Delphi process in 2018 and recommended the European Working Group on Sarcopenia in Older People (EWGSOP) original definition should be the preferred operational definition for use by clinicians and researchers. However, a subsequent revision to the EWGSOP definition in 2018 has led to calls for further work by the Task Force to clarify its consensus definition, and this may also present an opportunity to expand the process to include a wider range of stakeholders including clinicians, patients, funding bodies and community groups. This interactive discussion session led by Dr. Scott will invite audience members to comment on key topics highlighted in the earlier presentations by Dr Sim and Dr Zanker, and also to provide their own input into potential priorities for the Task Force, including developing consultation strategies, determining patient-relevant sarcopenia outcomes, and establishing local cut-points for components of sarcopenia. These discussions will be transcribed and subsequently reported to the Task Force to inform initiatives aimed at harmonising and promoting recommendations for sarcopenia case finding in Australia and New Zealand.

SYMPOSIUM 3 – SARCOPENIA OVER THE COURSE OF HOSPITALISATION: PREDICTIVE VALUE OF MUSCLE MEASURES

Predictive value of muscle measures during acute hospitalization of older adults: The EMPOWER study

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Background: Approximately 10% of older adults is annually admitted to a hospital. Hospitalized older adults are at risk for detrimental outcomes, such as falls and loss of self-dependency. Muscle measures may be used for identification for adults at risk, timing and targets for intervention.
Methods: The EMPOWER study is an observational, prospective, longitudinal inception cohort of 378 patients aged 70 years and older who were subsequently admitted to four wards of the VU University Medical Center (The Netherlands) between April and December 2015. Patients were assessed for demographic and clinical characteristics, measurements of muscle mass (by bioelectrical impedance analysis), handgrip strength (by dynamometry) both at admission and at discharge. Three months post-discharge, mortality, falls and ADL/IADL by the Katz and Lawton and Brody score were assessed by a follow-up telephone interview. Long-term mortality up to four years post-discharge was obtained from hospital registries.
Results: The mean age was 79.7 years (SD 6.39), 49% were female and the median length of stay was 5 days (IQR 3-8). The majority of patients were living independently at the time of hospitalization (90%) and three months post-discharge (83%). The prevalence of sarcopenia was 40% with a higher proportion of males (76%) compared to females (5%). Mortality was 14% and 49% respectively at three-month and four-year follow-up. Muscle measures showed no significant decline during the hospital stay but were significantly associated with falls, loss of ADL/IADL and short- and long-term mortality.
Conclusion: Muscle measures in older hospitalized older patients relate to both short- and long-term detrimental outcomes while the change of muscle measures during hospitalization is inconclusive. Muscle measures are suited to identify patients at risk and for the planning of dedicated pre- and

post-hospital interventions. Future prospective studies and trials are required to address the protective value of the aforementioned interventions.

Longitudinal changes of muscle mass, muscle strength and physical performance in acutely admitted older adults up to three months post-discharge: The Hospital-ADL study

JJ Aarden; EM Reijnierse; M van der Schaaf; M van der Esch; LA Reichardt; R van Seben; JA Bosch; JWR Twisk; AB Maier; BM Buurman; RHH Engelbert; On behalf of the Hospital-ADL study group
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Background: Over 30% of acutely hospitalized adults aged 70 and older experience decline in their activities of daily living, such as standing up from a chair or walking. The decline in activities of daily living is associated with low muscle mass and muscle strength. Information on the course of muscle mass, muscle strength and physical performance over time may provide specific starting points for timing and targets for intervention.
Methods: The Hospital-ADL study is a multicentre, observational, prospective cohort study of 401 patients aged 70 years and older who were acutely admitted to six hospitals in The Netherlands between September 2015 and June 2017. Patients were assessed for demographic, psychosocial and physical measurements including muscle mass (by bioelectrical impedance analysis), handgrip strength (by dynamometry), chair stand time and gait speed (by Short Physical Performance Battery) at admission, discharge and one- and three months post-discharge.
Results: The mean age of the patients was 79.3 years (SD 6.6) and 49% were female. Muscle mass and muscle strength did not change during the acute hospital stay but showed a significant decline after discharge from the hospital. Chair stand time and gait speed improved significantly from acute hospitalization up to three months post-discharge. Fear of falling showed an interaction effect with the course of muscle strength over time.
Conclusion: Muscle mass and muscle strength did not change during acute hospitalization. At post-discharge, a significant decline was found in muscle mass and muscle strength. Future studies should focus on improving muscle mass and muscle strength including psychological aspects such as fear of falling directly after discharge from hospital.

SYMPOSIUM 3 – SARCOPENIA OVER THE COURSE OF HOSPITALISATION: PREDICTIVE VALUE OF MUSCLE MEASURES

Muscle measures and its clinical determinants in subacute geriatric rehabilitation patients: The EMPOWER-GR study

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Background: Geriatric patients admitted to subacute rehabilitation are at high risk of sarcopenia due to muscle atrophy arising from their acute hospital admission and extended periods of bed rest during hospitalisation, in combination with older age and multimorbidity. In this context, sarcopenia may be a key determinant of functional rehabilitation outcomes.
Methods: The EMPOWER-GR study is an ongoing multicentre, observational, prospective longitudinal cohort of patients admitted to subacute geriatric rehabilitation wards. Our first wave of data included 693 patients. A Comprehensive Geriatric Assessment was performed assessing various health domains at admission and discharge, including muscle mass (by bioelectrical impedance analysis), handgrip strength (by dynamometry) and physical performance (by Short Physical Performance Battery; SPPB). A follow-up telephone interview was conducted three months post-discharge.
Results: The mean age was 82.2 years (SD 7.9), 57% were female and the median length of stay was 20 days (IQR 14-30). Before hospitalization, 97% was living independently. At admission, 63% was moderately-severely frail, 52% malnourished, 96% ADL dependent and the median SPPB score was 2 points (IQR 0-4). The prevalence of sarcopenia was 40% and the in-hospital incidence 7%. Skeletal muscle mass declined by –0.1±2.4kg. Handgrip strength, gait speed and SPPB score demonstrated improvements; handgrip strength by +0.7±4.4 kg, gait speed by +0.13±0.21 m/s and SPPB by +2±2 points. Muscle measures were significantly associated with inflammation, risk of malnutrition, functional

dependency during admission, and with institutionalization and mortality at three months post-discharge.

Conclusion: The high proportion with sarcopenia supports the importance of diagnosing sarcopenia in this setting and the need for further investigation of therapeutic strategies. Despite the minimal changes in muscle measures, there was substantive individual variation and a high incidence of sarcopenia. Collectively, these data support subacute care as an important setting for the implementation of sarcopenia diagnostics as well as preventive and therapeutic strategies.

SYMPOSIUM 5 – SPRINTT: MOVING TOWARD FUNCTION-CENTRED GERIATRIC MEDICINE

The "function vs. disease dilemma" in contemporary medicine: Physical frailty & sarcopenia as a prototypic condition of new-generation geriatric medicine. The message of the SPRINTT project

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Due to the worldwide demographic transition, healthcare systems are facing new demands. Health services—with their approach of mostly single acute conditions—are indeed confronted with an expanding older population characterized by specific medical needs related to multimorbidity and functional impairment. The European research project "Sarcopenia and Physical fRailty IN older people: multicomponenT Treatment strategies" (SPRINTT) project is specifically designed to overcome existing barriers for efficient public health interventions against frailty, and promote the implementation of successful aging strategies across Europe. The SPRINTT randomized clinical trial (RCT) will compare the efficacy of a multicomponent intervention (based on long-term structured physical activity, nutritional counselling, and an information and communication technology intervention) versus a Healthy Aging Lifestyle Education program for preventing incident mobility disability in community-dwelling older persons with physical frailty and sarcopenia. For the RCT, 1,500 community dwellers, aged 70 years and older (750 per treatment arm) will be enrolled. The study population will be comprised of "real life", non-disabled older persons exposed to increased vulnerability to stressors. The identification of such population will rely on three key elements: low muscle mass, measured by DXA; clinical signs of physical frailty (i.e., weakness, slow walking speed, and poor balance); absence of major mobility disability. The primary outcome will be the incidence of mobility disability (i.e., incident inability to walk 400 meters). Secondary outcomes will include, among others, changes in physical performance and function; ability of selected biomarkers to predict the rate of change in muscle mass; incidence of falls. The SPRINTT RCT will be conducted in 15 study sites located in nine European countries. The inclusion of a population with special needs will open pathways for future direction in the prevention of physical disability. In this symposium, the background, rationale, design, and data from the baseline visit of the SPRINTT trial will be described.

New strategies for biomarker discovery in the field of physical frailty and sarcopenia

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Physical frailty (PF) and sarcopenia are two common geriatric conditions upstream of the disabling cascade. The lack of a unique operational definition for PF and sarcopenia and their complex pathophysiology make the development of biomarkers for these conditions extremely challenging. Presently available biomarkers for PF and sarcopenia are typically related to specific pathogenic mechanisms and/or phenotypes. As such, they only describe single aspects of the conditions and are weakly associated with clinically relevant outcomes. This scenario suggests that there might not be one single biological marker that reliably tracks the multitude of different contributors and phenotypes of PF and sarcopenia. A shift of paradigm is therefore needed, moving from the quest for a single biomarker to the development of multivariate/multidimensional modeling of a panel of complementary biomarkers (likely within multiple classes: imaging, serum biomarkers, and functional tests). This approach may promote: (1) the early detection of otherwise subclinical conditions, (2) the diagnostic assessment of clinically manifested PF and sarcopenia, (3) the risk stratification of subjects with a suspected or confirmed diagnosis, (4) the tracking of the conditions over time, (5) the selection of an appropriate therapeutic intervention, and (6) the monitoring of the response to treatment. As opposed to conventional monodimensional approaches, the simultaneous evaluation of multiple parameters belonging to different domains may be better suited to cope with the heterogeneity of complex age-related phenomena, such as PF and sarcopenia.

Nutritional intervention against physical frailty and sasrcopenia

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Nutritional status is of course a major determinant of the person's wellbeing. Evidence suggests that nutrition represents an important and modifiable factor potentially affecting the frailty status of the older person. Nutrition is not only involved in the direct assessment of frailty, but may also play a role in the definition of the interventions aimed at restoring robustness and contrasting sarcopenia. Given its capacity to provide beneficial effects on multiple systems and at biological, clinical, and social levels, nutrition may be considered as a multicomponent intervention per se. Notably, the combination of nutritional interventions and physical exercise appears to be the most effective strategy presently available for the management of sarcopenia.
For a nutritional intervention to be effective against frailty and sarcopenia, it should: a) provide an adequate caloric intake; b) ensure the provision of appropriate nutrients, taking into account age, sex, health status, PA level, and comorbidities; c) provide the adequate quality and quantity of nutrients at the right time, that is, when physiologically needed. We will detail existing evidence on the efficacy of different combinations of macronutrient, micronutrient, and "nutraceutical" compounds alone and in combination with exercise in relation to skeletal muscle mass, metabolism (protein and fuel), and performance (i.e., strength and function).

SYMPOSIUM 6 – IMPACT OF EXERCISE ON CELLULAR CHANGES DURING NEUROMUSCULAR AGEING

Age-related neurodegeneration may be caused by defects at the nuclear envelope, and attenuated by exercise

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Extensions to lifespan have resulted in widespread frailty caused by loss of skeletal muscle mass. Many studies have shown that age-related loss of skeletal muscle is driven at least partly by denervation arising from death of motoneurons. Recent evidence indicates that degradation of the nucleocytoplasmic barrier and transport process are likely contributors to motoneuron death in normal ageing. It is well established that exercise protects muscle mass in old age, so we asked whether this outcome might be due to prevention of age-related degenerative changes in motoneurons. Mice were given access to a running wheel for four months (or were retained as sedentary controls), and we then used immunohistochemistry to examine nuclear envelope and nucleocytoplasmic transport proteins in their motoneurons. We found that loss of lumbar motoneurons in old age was accompanied by reductions in immunodetectable levels of key nucleocytoplasmic transport proteins in surviving neurons, but these changes were attenuated in elderly animals that had undergone wheel running. Our results show that exercise reduces some of the emergent defects at the nuclear envelope that contribute to age-related motoneuron death, and by reducing motoneuron death it potentially helps preserve muscle mass by reducing denervation atrophy.

Structural alterations at the myotendinous junction in elderly and exercised mouse skeletal muscles

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Progressive loss of muscle mass accompanied by decline in muscle function are cardinal features of sarcopenia. The myotendinous junction is a crucial interface between tendons and contractile elements, and alteration in the properties of this structure has the potential to impact significantly on muscle function. Therefore, we sought to investigate whether changes at the myotendinous junction might contribute to the age-related decline in muscle function, and whether regular exercise might reduce the severity of any change. We visualised the myotendinous junctions of soleus muscle fibres from young (n=5, 6 months), elderly sedentary (n=5, 24 months), and elderly exercised (n=5, 24 months) mice using whole-mount and transverse section immunohistochemistry. Length of the myotendinous region of muscle fibres increased by 95% between 6 and 24 months of age ($p<0.0001$) with no significant change in total fibre length or muscle pennation angle, resulting in a 6.4% decline in the contractile length of fibres. Extension to the myotendinous region was accompanied by a doubling (from 3% to 6% of section area) in collagen deposition in sections containing myotendinous profiles. Old mice that exercised regularly between 20-24 months reversed these changes. Therefore, prevention or reversal of changes to the connective tissue framework with regular exercise has

the potential to maintain or improve muscle function during normal ageing.

Proteomic differences between young, elderly, and exercised-elderly murine soleus muscles and their correlations with deficits in force production

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Skeletal muscles deteriorate with age and this manifests as weakness and disability amongst the elderly. To date, the most effective intervention against sarcopenia is exercise, but its mechanism of action at the cellular and molecular level has not been elucidated. Therefore, we sought to deepen our understanding of age-related changes in the C57Bl6 mouse soleus proteome and the potential impact these changes have on muscle force production. Moreover, we investigated how voluntary aerobic exercise acts to protect muscle function in sarcopenia and the concomitant impact it has on the soleus proteome.

We collected and measured the maximum absolute and specific force produced, muscle length vs tension relationships, stimulation frequency vs force, and nerve vs direct muscle stimulation of 29 soleus muscles (13 young, 10 elderly and 6 exercised elderly). A subset of this sample (3 young, 3 elderly and 3 exercised elderly) was subjected to proteomic analysis using SWATH-MS (sequential window acquisition of all theoretical fragment ion spectra mass spectrometry) to identify and quantify relative differences between the proteomes of young, elderly and exercised-elderly muscles, and whether they correlated with differences in force production characteristics. Furthermore, the subcellular location of proteins of interest was identified on tissue sections using fluorescence immunohistochemistry. The results of this investigation are currently pending and will be presented at this forum.