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A NOVEL NEM6 MOUSE MODEL REVEALS DISTINCT DISEASE PROGRESSION IN TWO PATHOGENIC VARIANTS OF KBTBD13

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Introduction: Nemaline Myopathy Type 6 (NEM6) is caused by dominant mutations in the KBTBD13 gene. Patients with NEM6 present with muscle weakness and stiffness, and histological analysis shows a core-rod myopathy.

Purpose: Previously, we studied the pathomechanism caused by the Dutch founder variant

Arg408Cys (R408C) using a homozygous knock-in mouse model. To better understand the function of KBTBD13 and the pathomechanism of NEM6, we recently developed a homozygous knock-in mouse model based on an Italian patient harboring a Gly67Arg (G67R) variant, who presents with a milder NEM6 phenotype.

Methods: In this model, we measured the maximum force generating capacity and relaxation time of hindlimb muscles and compared these to wildtype mice. We also performed histological analyses to study nemaline rods, mitochondrial cores and fiber type composition.

Results: The maximum force generating capacity is not reduced at 3 and 9 months of age, while muscle relaxation is significantly slower in knock-in mice compared to wildtypes. Interestingly, histological analyses revealed no pathology.

Conclusion: Taken together, these results suggest that impaired relaxation kinetics are an early- onset symptom of NEM6, and may therefore be a direct effect of KBTBD13 variants. More research into the function and variants of KBTBD13 is required to test this hypothesis. Investigations in 18 month old knock-in mice are in progress to further elucidate the pathomechanism of NEM6, as well as protein interaction studies to identify the function of KBTBD13.

Bone Phenotype in a Novel Mouse Model of Mild Haploinsufficient Osteogenesis Imperfecta

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Background: Osteogenesis Imperfecta (OI) is a genetic disorder causing bone fragility, with OI type 1 being the mildest form. It is caused by a deficiency of collagen type I due to *COL1A1* gene variants, leading to fractures. Despite representing >30% of OI patients, research has been limited by the lack of effective mouse models.

Purpose: This study aimed to develop and characterize a new mouse model for mild haploinsufficient OI.

Methods: A mild haploinsufficient OI (hiOI) mouse model was created using CRISPR/Cas9 to induce a heterozygous deletion of the entire *Col1a1* allele in C57BL/6J mice. 20 hiOI and 20 wild-type (WT) mice (50% males) were analysed at 8 weeks of age. The expression of collagen type I chains in bone and additional bone markers was investigated using RT-qPCR. Bone RNA sequencing was performed (n_{WT}=5; n_{hiOI}=5; males). Markers for bone formation (P1NP) and resorption (TRAcP 5b) were measured in serum with ELISA (n_{WT}=20, 50% males; n_{hiOI}=20, 50% males). Bone analysis included microcomputed tomography (µCT; n_{WT}=20, 50% males; n_{hiOI}=20, 50% males), histology (Masson Goldner's trichrome; n_{WT}=9; n_{hiOI}=9; males), and 3-point bending test (n_{WT}=18, 50% males; n_{hiOI}=13, 69% males).

Results: A significantly lower *Col1a1*/*Col1a2* ratio was found in hiOI mice, reflecting collagen deficiency. Increased expression of bone turnover markers highlighted the presence of a metabolic bone disorder. RNA sequencing revealed upregulation of 51 genes related to collagen biosynthesis and extracellular matrix formation. P1NP was significantly reduced and positively correlated with the *Col1a1/Col1a2* ratio. TRAcP was unaltered, indicating that osteoclast number was not impaired. µCT and histological analysis confirmed impaired bone structure in hiOI mice, and the 3-point bending test revealed reduced biomechanical properties, including force, deformation, energy, strain, stress and stiffness.

Conclusion: The hiOI mouse model mimics the mild haploinsufficient form of OI, making it a valuable tool for advancing research and therapies.

OSTEOGENESIS IMPERFECTA MAY AFFECT MECHANORESPONSIVENESS OF OSTEOCYTES IN THEIR NATIVE MATRIX

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Osteogenesis imperfecta (OI) is characterized by bone deformities and fragility as a result of reduced bone mass and altered bone matrix properties. Mechanosensitive osteocytes are embedded in the bone matrix and orchestrate bone adaptation to mechanical loading. This study aimed to investigate whether abnormalities in OI bone matrix affect the osteocyte response to mechanical loading. Osteocytes from 14 OI patients and 15 non-OI patients were either cultured isolated or in their native matrix in bone explants. Isolated osteocytes were treated by 1 h pulsating fluid flow (PFF), either or not followed by 6 or 24 h post-culture. Nitric oxide (NO) release, as a measure of mechanoresponsiveness, was quantified during PFF treatment. Bone explants containing osteocytes in their native matrix were mechanically loaded by three-point bending for 5 min, followed by 6 h post-culture. Bone stiffness and gene expression of mechanosensitivity-related genes such as cyclooxygenase-2 (*COX-2*), interleukin 6 (*IL-6*), endopeptidases on X chromosome (*PHEX*), and ring finger protein 213 (*RNF213*) were measured. Bone explants containing osteocytes in their native matrix were cultured for 18 h and 36 h for basal collagen type I alpha 1 chain (*COL1A1)* gene expression analysis. Results showed that the stiffness of non-OI and OI bone explants was similar.

Basal *COL1A1* gene expression in osteocytes in non-OI bone tended to decrease with time in vitro, while osteocytes in OI bone showed a constant gene expression. PFF increased NO release, *COX-2* and *IL-6* gene expression in both isolated non-OI and OI osteocytes, while osteocytes embedded in OI bone matrix showed a lower response to mechanical loading compared to non-OI osteocytes with 6 h post-culture. In conclusion, these data suggests that abnormalities in OI bone matrix may affect osteocyte mechanoresponsiveness, which could, at least in part, be responsible for bone fragility in OI.

THE ACUTE PHASE RESPONSE TO BURN INJURY: AN IN-SILICO MODELING APPROACH

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Background: Burn injuries cause complex events, such as acute inflammation, which play a crucial role in tissue repair and regeneration. The activation of the complement system after burn injury is essential to the inflammatory response and mediates various immune pathways during healing.

Objective: Develop and validate a computational model that simulates the acute inflammatory phase during the first 18 days post burn injury by using animal data.

Methods: Our Agent Based Cellular Potts model approach includes different cell types as individual agents, cytokines and growth factors that interact within a defined tissue environment on a two- dimensional wound simulation. This model considers systemic factors such as the concentration of cytokines and chemokines immune cell recruitment, and local factors including Damage Associated Molecular patterns that signal tissue damage. We incorporated experimental data from animal burn models from the literature to validate the interactions of key players within the acute inflammation cascade, seeking to create a representation of complement activation, inflammatory events and the associated consequences over time.

Results: Through simulation, we investigated how different factors, such as the severity of burn injury, the prolonged inflammation, and changes in the concentration of complement factors, affect the dynamics of the acute inflammatory phase. Furthermore, we explored the interaction between complement activation and other signalling pathways involved in burn wound healing, such as IL-6, IL-8, IL-1β, TNF-α and TGF-β1 concentration with increasing CRP concentration (in blood and wound) and complement activation.

Conclusion: This computational model provides insight into the spatio-temporal dynamics of acute inflammation driving factors after burn injuries.

Untargeted Metabolomics Analysis in Skeletal Muscle: Metabolite Alterations in Skeletal Muscle of Long COVID Patients

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Introduction Long COVID poses a substantial risk to healthcare demands in the coming years. Patients show metabolic shifts toward glycolysis, reduced capillary-to-fiber ratios, increased glycolytic fibers, necrosis, atrophy, and leukocyte infiltration in skeletal muscle, potentially contributing to exercise intolerance and muscle pain. However, many metabolites within skeletal muscle involved in these changes remain unexplored.

Purpose This study aims to establish an optimized untargeted metabolomics pipeline to identify novel metabolites in skeletal muscle associated with muscle abnormities in long COVID. The objective is to address metabolite heterogeneity among individuals by refining the analysis protocol and selecting long COVID patients most representative of muscle abnormities for analysis.

Method Vastus lateralis biopsies were collected and analyzed for metabolite abundance using liquid Chromatography–mass spectrometry. Principal component analysis and K-Medoids were performed to cluster subjects based on their metabolite profiles, yielding 14 long COVID patients and 12 healthy controls for further, deep phenotyping. Metabolomic data was analyzed using MetaboAnalystR and pathway-specific metabolite abundance was assessed by integrating data from databases such as HMDB, KEGG, and RaMP.

Results Untargeted metabolomic analysis revealed 274 metabolites with group differences (Fig. 1) based on unadjusted p-values, but only 6 metabolites (citric acid, pyruvic acid, methyl hydrogen fumarate, FAD, sorbitol, and ADP-ribose 1-2 cyclic phosphate) were significantly downregulated in long COVID (FDR < 0.05). Our results show downregulation of tricarboxylic acid cycle metabolites in long COVID. Conversely, the greater glycolytic metabolite abundance suggests possible compensation for a likely impaired polyol pathway, indicated by lower sorbitol levels in patients. Moreover, reduced tRNA splicing activity in skeletal muscle of long COVID patients is suggested by notably low levels of ADP-ribose 1-2 cyclic phosphate, a unique molecular marker of this process.

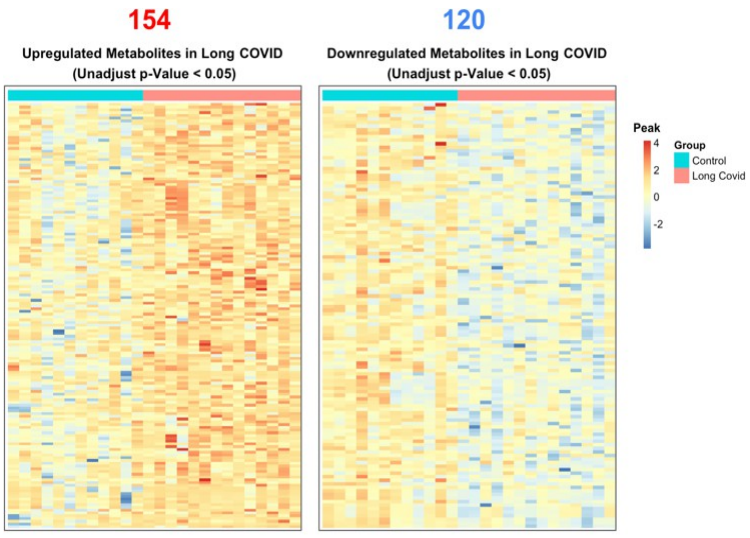

Figure 1. Heatmap illustrating distinct patterns of upregulated and downregulated metabolites in long COVID group

Conclusions Our newly developed untargeted metabolomics pipeline allows for the identification of long COVID patient phenotypes based on the metabolites profile in skeletal muscle. Our analysis identified metabolites associated with muscle abnormalities in long COVID, and highlights new directions to investigate cellular pathways that underlie the physiological change in skeletal muscle.

ESTIMATING *IN VIVO* SKELETAL MUSCLE OXIDATIVE AND DIFFUSIVE CAPACITY VIA NEAR INFRARED SPECTROSCOPY

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Introduction: Recently, Pilotto et al.[1] established a technique to non-invasively estimate *in vivo* muscle oxidative and diffusive capacity using near infrared spectroscopy (NIRS), which has great potential to provide insights into the physiological determinants of exercise capacity. However, there is a paucity of data pertaining to the reliability and validity of this method. **Purpose:** This pilot study aimed to determine the reliability of estimating oxidative and diffusive capacity via NIRS and provide further physiological validation of this technique.

Methods: Ten participants (7 males, 3 females, age 34±16 years, maximal oxygen uptake [$\dot{V}O_{2max}$] 46.6±10.3 ml.min^{-1}.kg^{-1} and peak power output [PPO] 4.5±1.2 W.kg^{-1}) participated. Oxidative and diffusive capacity were assessed using procedures described by Pilotto et al.[1], with the exception that an intermediate tissue saturation index (TSI) range was added. The recovery rate constant *k* in HIGH (k_{HIGH}) reflected mitochondrial oxidative capacity, whereas k_{LOW}/TSI_{LOW} was used as a proxy for diffusive capacity. Vastus lateralis muscle biopsies were assessed for mitochondrial oxidative phosphorylation (OXPHOS) capacity via high-resolution respirometry.

Results: *Validation:* Participants displayed an *ex vivo* OXPHOS capacity of 97.4±32.5 pmol.s^{-1}.mg^{-1}. k_{HIGH} (3.43±0.46 min^{-1}) was correlated with $\dot{V}O_{2max}$ (r=0.89, p<0.001, Fig. 1A) and PPO (r=0.88, p<0.001), but not with OXPHOS capacity (r=0.25, p=0.491). Both k_{MID} (3.29±0.78 min^{-1}) and k_{LOW} (2.22±0.45 min^{-1}) were correlated with $\dot{V}O_{2max}$ (r=0.68, p=0.030 and r=0.77, p=0.009, respectively) and PPO (r=0.72, p=0.019 and r=0.83, p=0.003, respectively). k_{LOW}/TSI_{LOW} (0.04±0.01 min^{-1}.%$^{-1}$) was correlated with $\dot{V}O_{2max}$ (r=0.84, p=0.003, Fig. 1B) and PPO (r=0.83, p=0.003) but not with OXPHOS capacity (r=0.52, p=0.127). *Reliability:* Repeated measures ANOVA showed that *k*-values did not differ between repeated measurements performed on three separate days (k_{HIGH} p=0.248, k_{MID} p=0.309, k_{LOW} p=0.251). The coefficient of variation (CV) of k_{HIGH} was 11.0%, k_{MID} was 8.2%, k_{LOW} was 13.3%, and k_{LOW}/TSI_{LOW} was 9.8%.

Conclusion: These preliminary findings indicate a good within-subject reliability of the occlusion protocol. They also suggest that NIRS-derived measures *in vivo* oxidative and diffusive capacity correlate well with *in vivo* aerobic function.

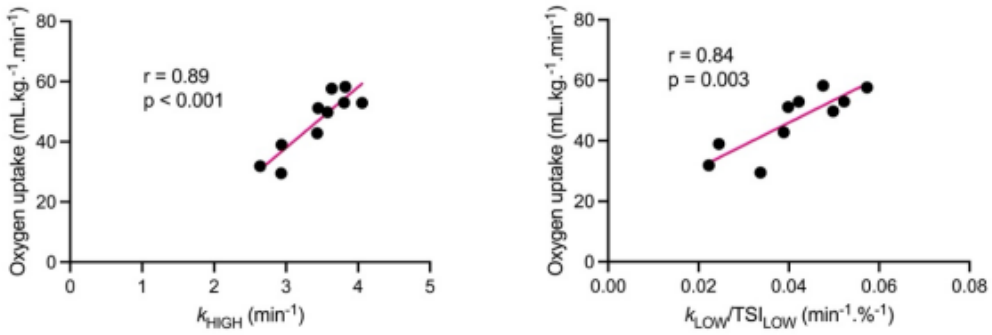

Figure 1 shows the correlations between k_{HIGH} (**A**) and k_{LOW}/TSI_{LOW} (**B**) with $\dot{V}O_{2max}$, respectively.

[1]*Pilotto AM et al. (2022). J Physiol 600, 4153–4168.*

IN VITRO DEVELOPMENT OF A HUMAN BURN WOUND MODEL: EXPLORING PARTIAL AND DEEP BURNS IN RECONSTRUCTED HUMAN SKIN

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Introduction Burn wound healing and deepening involve complex mechanisms that are still not well understood. To get a better insight in these mechanisms there is need for human based models.
Purpose Our aim was to develop an *in vitro* burn wound model, with partial-thickness and deep burns in a three-dimensional (3D) reconstructed human skin (RhS) model and establish wound healing properties over time.
Method Standard tissue engineered RhS consisting of human cell populated epidermal and dermal compartments, were used to mimic the human skin *in vitro*. Burn wounds were applied using a soldering iron at 70°C, 110°C or 140°C for 30 seconds. RhS samples were analyzed on days 1, 3 and 7 post-burn using (immuno)histochemistry for wound depth (hematoxylin and eosin staining), activation (vimentin, fibroblast activating protein (FAP)), myofibroblasts (α-smooth muscle actin (α-SMA)) and cell proliferation (Ki67). Secretion of Neutrophil gelatinase-associated lipocalin(NGAL), matrix metalloprotease(MMP) 9, Serum Amyloid A(SAA), and Intercellular Adhesion Molecule 1(ICAM-1) was measured using ELISA.
Results RhS with 70°C burn injury showed no tissue damage, while 110°C and 140°C burns indicated re-epithelialization within one week. Vimentin staining showed a scarcely populated dermal wound edge, indicative for post-burn fibroblast migration. FAP stained in the lower dermal wound edge showing more papillary fibroblasts. One week post-burn, fibroblast proliferation(Ki67) and myofibroblast(α-SMA) differentiation in the wound edge was observed. Significantly increased levels of secreted MMP-9, ICAM-1, and NGAL were found in burned RhS compared to control.
Conclusion We successfully generated an *in vitro* human burn wound model mimicking different burn depths with concurrent wound healing properties, that will serve as a basis to study burn wound deepening.

IGF-1 and TGF-β1 synergistically stimulate collagen formation in C2C12 myoblasts and Myotubes

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Abstract:

Maintaining adequate and appropriate collagen formation is essential for muscle health and the maintenance of athletic performance. However, dysregulated growth factors due to various causes can lead to excessive collagen deposition and muscle fibrosis, thereby impairing muscle function. Transforming Growth Factor β1 (TGF-β1) and Insulin-like Growth Factor 1 (IGF-1) play crucial roles in muscle recovery, with TGF-β1 promoting fibroblast activation and collagen synthesis, while IGF-1 supports cell proliferation, differentiation, and protein synthesis. However, their combined effects on collagen formation in muscle stem cells are rarely understood. This study aimed to explore their **i**ndependent and synergistic effects.

Using the C2C12 mouse myoblast cell line, we treated the cells in four different ways: with 100ng/mL IGF-1, 10 ng/mL TGF-β1, neither, or a combination of IGF-1 and TGF-β1. The results of immunofluorescence showed that IGF-1 enhanced cell proliferation, while TGF-β1 did not. The collagen staining was intensified in the combined treatment group with TGF-β1 and IGF-1, and the semi quantitative results showed that the difference was statistically significant. The qPCR results showed that TGF-β1 upregulated fibrosis-related genes, which was moderated by IGF-1. Interestingly, IGF-1 and TGF-β1 synergistically promoted the expression of COL-1 in myotubes at 48 hours. IGF-1activated the AKT pathway, whereas TGF-β1 activated Smad2. Notably, TGF-β1 attenuated IGF-1'spromotion of myotube fusion and size.

In conclusion, although IGF-1 and TGF-β1 play different roles in the proliferation and differentiation of C2C12 cells, both growth factors promote collagen synthesis. Their interplay influences muscle regeneration dynamics, making it essential to understand these interactions to regulate fibrosis and preserve muscle.

Keywords: Muscle regeneration, Collagen, Fibrosis, TGF-β, IGF-1

LIPOFUSCIN AS A MARKER FOR SKELETAL MUSCLE BIOLOGICAL AGE

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Introduction: Aging is associated with reduced skeletal muscle mass and function, but different people age at different rates. The use of biological age is therefore thought to be a better indicator of a person's health than chronological age. Recent evidence suggests that a loss of proteostasis is a hallmark of aging. Lipofuscin is an intracellular accumulation of lipid-containing residues of lysosomal digestion. It is formed as a byproduct of oxidative stress and the degradation of damaged cellular components, particularly under conditions of impaired autophagy or proteasomal function, limiting metabolic efficiency. Lipofuscin accumulates progressively in neurons and cardiomyocytes with advancing age, but whether this also happens in skeletal muscle with age is unclear

Purpose: To investigate the accumulation of lipofuscin in skeletal muscle as a marker of biological age in health, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Long COVID patients.

Method: In this study, we studied the accumulation of lipofuscin in the vastus lateralis muscle in relation to the biological age of 30 healthy participants and compared this with muscle biopsies from patients with chronic diseases, associated with oxidative stress, including long COVID (n=24), and ME/CFS (n=26). Immunohistochemistry and electron microscopy were used to assess lipofuscin accumulation in skeletal muscle.

Results: Our initial results (n=16 healthy controls) show that lipofuscin accumulation in skeletal muscle increased with chronological age (P=0.002, R^2=0.50, age range: 18-63 years). Our young cohort (>39.5 years) showed on average 0.13±0.21/fiber, whereas the older cohort (>39.5 years) showed 1.00±0.48/fiber, P=0.001).
Lipofuscin accumulation was higher in patients with long COVID (P=0.010) and with ME/CFS (P<0.001) compared to healthy controls. The age-dependent relation was however absent in patients with Long COVID (n=6, P=0.68) and ME/CFS (n=4, P=0.28). Compared to the association in the healthy controls, the expected ("biological") age was ~74 years, despite their chronological age of 47 years.

Conclusion: These results suggest that long COVID and ME/CFS are associated with an increased accumulation of lipofuscin, similar to advanced or accelerated aging. Our preliminary data hint to lipofuscin-linked accelerated aging of skeletal muscle in Long COVID and ME/CFS and shows the potential of lipofuscin as a physiological biomarker of muscle aging.

DEVELOPMENT OF A NOVEL 3D *IN-VITRO* MODEL OF MECHANICALLY LOADED CARTILAGE-LIKE TISSUE

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Introduction The development of novel treatments for temporomandibular joint disorders is hampered by a lack of *in vivo-mimetic* preclinical models allowing three-dimensional (3D) cell culture and mechanical stimulation, which both strongly affect cell behavior, such as the response to soluble factors meant to aid regeneration of cartilage.

Purpose Our aim is to establish a novel 3D *in-vitro* model of mechanically loaded cartilage-like tissue.

Method Mouse bone marrow stem cells (mBMSCs) were cultured up to 7 days as cylindrical constructs (Θ 6 mm, height 3-7 mm) containing 10^6 cells/ml agarose, in proliferation medium consisting of Dulbecco's modified Eagle's medium (DMEM) with 10 % fetal bovine serum (FBS), or in differentiation medium consisting of high-glucose DMEM with 10^{-7} M dexamethasone, 50 µg/ml ascorbate-2-phosphate, 40 µg/ml proline, 100 µg/ml pyruvate, and 50 mg/ml ITS/Premix. Dynamic mechanical loading (5% compression at 1Hz), and constant loading (10%, 20% and 30% compression) were applied for 20 min (Fig.1). Non-loaded samples served as controls. Cell death (live-death staining), Prestoblue assay and gene expression (qPCR) were measured at day 1, 4, and 7.

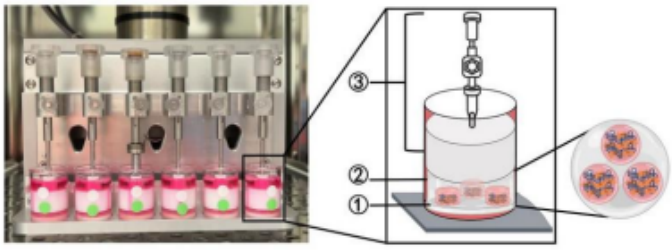

Fig.1 The 3D model involves three parts: ① The porous glass filter disc used for gas-liquid exchange. ② The 3% agarose construct (diameter: 6mm, height: 3 to 7mm) containing cells in 3D. ③ The mechanical compressive loading is applied on the agarose constructs using a dynamic loading device, consisting of a computer-driven voice coil linear microactuator. The contains cell culture medium.

Results The 3mm construct contained ~2-fold more viable mBMSCs compared to the 5mm and 7 mm constructs. Differentiation medium enhanced *Sox9* gene expression in mBMSCs compared to proliferation medium (2.4-fold), but did not affect Aggrecan or Collagen type 2 expression. Constructs of 3mm height in proliferation medium were used for loading experiments. 30% constant strain damaged the agarose constructs. 20% constant strain reduced the number of live cells compared with 10% constant strain. 5% dynamic strain enhanced c-Fos gene expression by 2.2-fold compared to 30% constant strain, and 10% and 20% constant strain enhanced c-Jun gene expression by 1.6-fold and 1.5-fold compared to control.

Conclusion The novel 3D *in-vitro* mechanically loaded cartilage-like tissue model was successfully established, laying the foundation for future studies on chondroinductive agents and mechanical loading.

POLYPHARMACY, FOR TREATING HYPERCHOLESTEROLEMIA AND INSULIN RESISTANCE, MITIGATES SKELETAL MUSCLE ATROPHY BUT REDUCES MITOCHONDRIAL RESPIRATION CAPACITY

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Introduction: Polypharmacy is common among elderly individuals who take multiple medications per day, but it is associated with adverse health outcomes. Statins, for hypercholesterolemia, and metformin, for Type 2 Diabetes Mellitus (T2DM) patients, are often combined. However, the effects of the combination on skeletal muscle have never been studied.

Purpose: This study aims to investigate the combined effects of statins and metformin in an isolated microenvironment with C2C12 skeletal muscle cells, and to explore changes in mitochondrial function in these C2C2 cells.

Methods: C2C12 myoblasts were cultured and differentiated into myotubes. Cells were treated with simvastatin (10 µM), metformin (50 µM or 1000 µM) or combined for 24-72h. Proliferation rate was assessed by the EdU assay, and myofiber diameter were measured. Mitochondrial networks were visualized by MitoTracker to observe morphological changes in mitochondria. Mitochondrial respiration was performed to measure mitochondrial respiration.

Results: Simvastatin treatment leads to atrophy in myotubes, which is mitigated by metformin treatment. The observed mitigation of the cytotoxic effects of simvastatin by metformin in myotubes, was not seen in myoblasts. Mitochondrial network not affected by the combination. Decreased routine respiration, maximal respiration and ATP production rate with the combined treatments suggest that mitochondrial respiration was negatively affected.

Conclusions: Simvastatin and metformin have different effects on skeletal muscle size and mitochondrial function. This research provides a mechanism of the microenvironmental effects of two inexpensive, preventative, commonly used medications, and could contribute to a better understanding in combining these drugs in patients.

SYSTEMIC UPREGULATED INFLAMMATORY CYTOKINES TNF-A, IL-6, AND IFN-Γ IN ESTABLISHED RHEUMATOID ARTHRITIS PATIENTS AFFECT MUSCLE MITOCHONDRIAL RESPIRATION

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Background

Despite anti-inflammatory treatment, patients with established rheumatoid arthritis (RA) often experience muscle fatigue, affecting up to 60% of cases and contributing to functional decline. Muscle fatigue, defined as the inability to sustain force over time, is not solely due to reduced muscle size but also involves intramuscular impairments. Dysfunctional mitochondrial respiration, crucial for ATP production and muscle endurance, may play a key role. Elevated inflammatory cytokines in RA, such as TNF-α, IL-6, and IFN-γ, have been implicated in mitochondrial dysfunction, but their exact effects remain unclear.

Purpose

The purpose of this study was to investigate how TNF-α, IL-6, and IFN-γ, at concentrations relevant in established RA, impact muscle mitochondrial respiration, muscle size, and muscle mitochondrial gene expression in vitro.

Methods

Human primary muscle cells were cultured, differentiated into myotubes, and exposed for 72 hours to TNF-α, IL-6, or IFN-γ (0, 10, 20, 40, or 160 pg/mL). Cytokine concentrations were based on RA patient serum from the Amsterdam UMC biobank and literature. Mitochondrial respiration was assessed using Seahorse respirometry, measuring basal, leak, ATP-linked, and maximal respiration. Myotube diameter was analyzed via brightfield microscopy, and mitochondrial gene expression was quantified via qPCR.

Results

TNF-α increased maximal respiration at 10 pg/mL but reduced it at 160 pg/mL. It also decreased myotube diameter by 22%. IL-6 followed a similar dose-dependent trend in maximal respiration and increased leak respiration, yet did not alter myotube size. Moreover, IL-6 reduced expression of mitochondrial genes NDUFA4 and COX4I1 by 23% and 32%, respectively. IFN-γ had no effect on myotube size but increased leak respiration at 10 and 20 pg/mL.

Conclusions

TNF-α and IL-6 impact mitochondrial respiration, while IL-6 and IFN-γ affect leak respiration, with IL-6 impairing mitochondrial gene expression. These findings highlight cytokine-mediated mitochondrial dysfunction as a potential contributor to muscle fatigue in RA, despite treatment. Further research is needed to understand the role of TNF-α and IFN-γ in mitochondrial gene expression.

AN IN VIVO RAT LUMBAR SPINE INSTABILITY MODEL INDUCED BY INTERVERTEBRAL DISC INJURY

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Introduction. Intervertebral disc (IVD) degeneration is a potential contributor to low-back pain. Experimental IVD disruption has been widely used to induce IVD degeneration in animal models[1,2], but different methods have been applied. It has been shown that IVD disruption in the short-term results in structural changes[3], but the early mechanical consequences and their correlation with structural changes remain unclear.

Purpose. (1) To establish a rat model of lumbar spine instability via IVD injury. (2) To investigate the relationship between changes in the structural and mechanical IVD properties. (3) To assess adaptations in low back musculature following IVD injury.

Method. Thirty-one adult male Wistar rats were randomly assigned to three groups: IVD knife stab lesion (knife, n=8), IVD needle puncture (needle, n=14), and sham surgery control (control, n=9). In the knife and needle groups, L4/L5 IVDs were injured at 14 weeks of age (**Fig.1**). One-two weeks post-intervention, lumbar multifidus (MF) and medial longissimus (ML) muscles were excised, L4-L5 spinal segments were harvested to assess mechanical properties indicative of spine stability, and IVDs were collected for histological analysis.

Results. Morphological changes were observed in both injury groups (**Fig.2**). IVD height and cross-sectional area did not differ between groups, but the needle group had a smaller nucleus relative to annulus area compared to controls. The needle group exhibited lower peak stiffness, peak moment, and hysteresis than controls in flexion, with no differences in left and right bending. No significant correlations were found between IVD structural and mechanical properties. The needle group showed higher normalized ML mass, while normalized MF mass was not different between groups.

Conclusions. A rat model of lumbar spine instability was successfully established via IVD needle injury. No significant correlations were found between IVD structural and mechanical properties. Only following IVD needle puncture, muscle adaptations were observed.

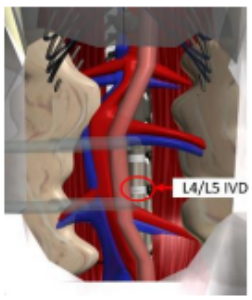

Figure 1. Schematic of intervertebral disc injury surgical approach.

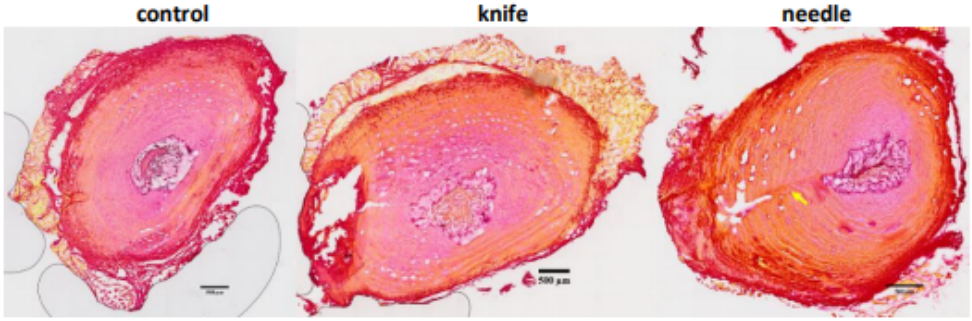

Figure 2. Examples of sections of the intervertebral disc stained with Picrosirius Red. Less organized annuls fibrosus (AF), less round-shaped nucleus pulposus (NP), and less clear border between AF and NP were observed in the knife and needle groups. Yellow arrow points to the needle puncture tract. Scale bar=500 µm

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Oxygen Delivery Deficits and Microvascular Abnormalities in Skeletal Muscle of ME/CFS and Long COVID Patients

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Introduction: Exercise is widely acknowledged as a vital component of health, enhancing physical fitness, mental well-being, and metabolic resilience. But what happens when movement, instead of rejuvenating, exacerbates fatigue and pain? In post-infectious diseases like Post-COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), even minor physical or mental exertion may result in overexertion, extreme fatigue, muscle pain, and worsening of other symptoms. These symptoms suggest a failure in the body's adaptive responses to maintain metabolic homeostasis during stress. Ineffective matching of oxygen delivery ($\dot{Q}O_2$) to consumption ($\dot{V}O_2$), as well as misalignment of energy substrates with local metabolic needs, is thought to play a central role in the disrupted metabolic homeostasis, contributing to the onset of overexertion and muscle fatigue. Therefore, this study focuses on skeletal muscle oxygenation, assessing local perfusion and diffusion.

Methods: Skeletal muscle biopsies from the vastus lateralis were obtained prior to a maximal exercise test in Post-COVID (n=24), ME/CFS (n=26), and healthy controls (n=30). During exercise, pulmonary gas exchange was measured using incremental ramp cardiopulmonary exercise tests (CPET), and muscle oxygenation was measured using near-infrared spectroscopy (NIRS). Immunohistology and electron microscopy were performed to assess muscle microvasculature structure and function, including capillarization, collagen IV content, nitric oxide synthetase (NOS) content, and markers of microdamage.

Results: Both Post-COVID and ME/CFS patients exhibited lower $\dot{V}O_{2,max}$ and peak power output, with no alterations in maximal heart rate or ventilatory equivalents. Simultaneously, patients tended to show signs of a peripheral muscle oxygenation deficit (*p=0.0804*). ME/CFS patients exhibited a significant reduction in capillary density (382±72, 378±70, 308±47, *p=0.0003*) and capillary-to-fibre ratio (2.1±0.6, 1.7±0.5, 1.5±0.5, for controls, Post-COVID, and ME/CFS, respectively; *p=0.0005*). In addition, both patient groups showed notable thickenings of the capillary basement membranes (2.0±0.2, 2.8±0.4, 2.8±0.3 µm, *p<0.0001*) alongside indications of endothelial dysfunction, such as endothelial morphological thickening, likely affecting oxygen diffusion.

Conclusion: The observed microvascular adaptations in both conditions may disrupt effective peripheral oxygenation in skeletal muscle, potentially disturbing metabolic homeostasis, contributing to fatigue and post-exertional malaise.

QUANTIFYING MECHANICAL AND MORPHOLOGICAL PROPERTIES OF PLANTAR FOOT SOFT TISSUES: A SYSTEMATIC REVIEW OF TECHNIQUES AND THEIR CLINIMETRIC PROPERTIES

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Introduction Diabetes-related foot ulcers contribute to significant morbidity and amputation risk. The mechanical (stiffness, elasticity) and morphological (thickness) properties of the plantar soft tissues play a role in distributing mechanical stresses and ulcer development. Nevertheless, it remains unknown which measurement technique has the best clinimetric attributes to quantify these properties, which is essential for ulcer prevention.

Purpose This systematic review aims to investigate the existing measurement techniques and determine which demonstrate the best clinimetric attributes (reliability, validity, and repeatability) to assess the mechanical and morphological properties of plantar foot soft tissues.

Method Following PRISMA guidelines, we systematically searched MEDLINE, EMBASE, and Web of Science for studies assessing plantar soft tissues' properties in adults. We included studies investigating clinimetric properties and used published cut-off data to interpret reliability, validity, and repeatability assessments. Methodological quality was evaluated using the COSMIN Risk of Bias tool.

Results From 3,857 screened studies, 127 evaluated plantar soft tissues' mechanical and/or morphological properties, with 36 investigating clinimetric properties. Ten techniques assessed mechanical properties, and six examined morphological properties. Reliability (27/36) and repeatability (23/36) were frequently reported, while validity was assessed in only four studies. Only Ultrasound (US) and Shear Wave Elastography (SWE) had both reliability and validity comprehensively investigated. US showed good-to-excellent intra-rater (ICC = 0.75–0.99) and inter-rater (ICC = 0.70–0.93) reliability, with moderate-to-strong validity (r = 0.5–1.0) compared to MRI and radiography. SWE showed excellent intra-rater reliability (ICC > 0.90) and strong validity (R^2 = 0.91) but had systematic measurement bias. Magnetic Resonance Elastography (MRE) showed promise to assess viscoelasticity but remains underexplored. Key methodological limitations included high operator dependency, inconsistent statistical methods, and poor blinding of assessors.

Conclusion The limited assessment of clinimetric properties complicates inter-study and inter-technique comparisons. US and SWE emerged as reliable and valid techniques, with MRI used as a reference for morphological assessments. Indentation-based techniques fail to assess viscoelasticity, while MRE could address this limitation but requires further validation. More research into the validity and reliability of methodologies is needed to identify the most reliable, valid and repeatable technique to quantify plantar soft tissue morphological and mechanical properties.

How Biomechanical Factors Influence the Development of Osteochondral Lesions of the Talus: A Narrative Review.

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ABSTRACT

Background: Osteochondral lesions of the talus (OLTs) are common ankle injuries, often caused by a sprain in the ankle joint and potentially leading to ankle osteoarthritis. While biomechanics plays an important role in joint motion and health, the literature on the role that biomechanical factors play in the development of OLTs is fragmented.

Objectives: The aim of this narrative review is to synthesize the current knowledge on the biomechanical factors that contribute to the development of OLTs.

Methods: Three databases PubMed, EMBASE (OVID) and Sportdiscus (Ebsco) were searched from their inception to March 26th, 2024, for studies about biomechanical factors in OLTs or biomechanical considerations in the development of OLTs.

Results: A total of 1946 studies were retrieved from the databases, and 21 studies were included in this literature. Results from the reviewed studies showed that 1) Significant differences in bone density and penetration strength as well as cartilage thickness and stiffness affect load distribution and stress concentration within the joint, especially at the medial and lateral edges of the talus, indicating that these areas are most susceptible to lesions due to greater loading and reduced regenerative potential; 2) Traumatic injury is the main cause of OLTs, particularly ankle inversion sprains. This may lead to acute and chronic osteochondral damage as well as repetitive microtrauma. Cartilage cracks that extend into the subchondral bone following trauma can lead an inadequate repair response, synovial fluid is squeezed into the cracks under load, eventually forming cysts and causing osteochondral damage; 3）Biomechanical movements and internal and external rotational transitions during the gait cycle produce significant stresses in the ankle joint, altering the loading pattern, and the repetitive nature of these movements may increase cartilage wear and lead to the development of OLTs; 4) Load distribution within the ankle joint has an important impact on the development of OLTs. Stress is usually concentrated around the defect area, and larger defects lead to reduced intra-articular contact area and increased stress, further aggravating lesion progression; 5) Ligament instability and muscle weakness can cause changes in the location of peak stress in the ankle joint, resulting in suboptimal loading patterns and cartilage wear.

Conclusions: After trauma, the progression of OLTs is greatly influenced by the structural integrity of the subchondral bone plate and the distribution of thickness and stiffness of the ankle cartilage. Uneven talus bone density and cartilage thickness make the medial and lateral aspects of the ankle cartilage more susceptible for injury. In addition, high stress and repetitive motion from internal and external rotational transitions in the gait cycle, ankle sprains, ligament instability, and muscle weakness may alter the mechanical loading pattern of the ankle joint. Suboptimal load distribution may increase the size of the defect and concentrate pressure on its edges, potentially raising pressure in that area and accelerating the progression of OLTs. Future studies could explore how gait dynamics affect OLTs development, leading to a better understanding of its biomechanics and improving prevention and rehabilitation strategies.

INVESTIGATING THE EFFECT OF PRE- AND POST-MENOPAUSAL IGF-1 CONCENTRATION ON SKELETAL MUSCLE MASS IN VITRO

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Background

Menopause marks the permanent end of menstrual cycles due to the cessation of ovarian follicular activity. It induces a decline of systemic circulating concentrations of growth factors including insulin-growth factor (IGF-1). Menopause is also associated with an increased risk to develop sarcopenia: a progressive and age-related decline in skeletal muscle mass which is leading to decreased muscle strength, increased risk of falls and disabilities. The complexity of menopause fluctuations in IGF-1 and the pathophysiological effects on skeletal muscle mass are not yet fully understood. Moreover, *in-vitro* models that mimic pre- and postmenopausal conditions remain poorly characterized.

Purpose

Investigate and compare the effect of IGF-1 (100 ng/ml) on muscle mass and gene expression of genes related to cell-proliferation, protein synthesis and protein degradation in three different *in-vitro* skeletal muscle models.

Method

Human induced Pluripotent Stem Cells (iPSCs)-derived myoblasts, primary human myoblasts, or immortalized mouse myoblast (C2C12) were cultured in DMEM with 10% fetal calf serum (FCS),and differentiated into muscle-fibers (myotubes) using 2% horse serum. Myotubes were incubated with or without IGF-1 (100ng/ml) to mimic pre- and post-menopausal IGF-1 conditions (N=6/ group). Bright-field images were taken to measure myotube diameter, as outcome measure for muscle mass. Gene expression was assessed for muscle cell-proliferation (CCND1, PKM2), protein synthesis (PHFDH) and protein degradation (TRIM63, FBXO32 and MYC) with qPCR (N=6/ group).

Results

IGF-1 had no effect on the diameter or gene expression of iPSC-derived myotubes compared to control conditions. In primary human myotubes, IGF-1 increased diameter by 13.9% and upregulated CCND1 (*$p<0.05$), with a trend toward decreased FBXO32 ($p=0.08$) compared to control. In C2C12 myotubes, IGF-1 significantly altered gene expression: FBXO32, MYC, and TRIM63 were downregulated, while PHGDH, PKM2, and CCND1 were upregulated (**$p<0.01$). The gene-expression differences in C2C12 compared to control were greater than those observed in primary human myotubes.

Conclusion

This study demonstrated *in-vitro* muscle model-specific differences in IGF-1 sensitivity between iPSC, human primary and C2C12 myotubes. These findings emphasize the need for further optimization of *in-vitro* skeletal muscle models to better replicate pre- and post-menopausal conditions and improve the knowledge of IGF-1's role in menopause-associated loss of muscle mass.

CALF MUSCLE LENGTH ADAPTATIONS TO FUNCTIONAL POWER TRAINING IN CHILDREN WITH CEREBRAL PALSY: A DOUBLE-BASELINE DESIGN

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Introduction: Children with spastic cerebral palsy (SCP) can experience leg muscle weakness, spasticity and muscle shortening. These impairments affect their gait pattern and their ability to walk and run, hindering participation in daily life activities. A 12-week functional power training with high-velocity exercises, has shown to improve walking and running ability [1]. Conventional strength training has been shown to increase muscle stiffness [2], potentially aggravating muscle shortening. However, we hypothesize that power training may maintain or even increase muscle belly and fascicle length, as the exercises might elicit eccentric contractions that promote the addition of sarcomeres in series [3].

Purpose: This study aimed to compare the effects of a functional power training program with usual care on gastrocnemius medialis (GM) muscle length in children with SCP.

Method: Twenty-two children with SCP (average age 8.8±2y) participated with three repeated measures at twelve weeks before the training (T0), just before the training (T1), and after completion of the training (T2). Isometric GM strength was assessed at T1 and T2. Walking and running speed were assessed with the 1-minute walk test and the muscle power sprint test at T1 and T2. GM muscle belly, tendon, and fascicle length were obtained using 3D ultrasound [4] at T0, T1 and T2. Isometric muscle strength (T1 vs T2), walking and running speed (T1 vs T2), and muscle belly, tendon, and fascicle length changes (ΔT1-T0 vs. ΔT2-T1), were compared using paired t-tests.

Results: Isometric muscle strength increased with 19% (T1: 161±87Nm, T2: 191±111Nm, $p<0.001$) after completion of the training (T2) compared to T1. Both walking (T1: 1.3±0.3m/s, T2: 1.5±0.2m/s) and running speed (T1: 2.9±0.6m/s, T2: 3.2±0.8m/s) increased with 14% ($p<0.001$). No significant differences were observed in muscle belly (ΔT1-T0: 2.3±3.5mm, ΔT2-T1: 1.2±3.7mm, $p=0.5$), tendon (ΔT1-T0: 0.9±3.1mm, ΔT2-T1: 1.7±3.9mm, $p=0.9$), and fascicle length change (ΔT1-T0: 1.8±4.9mm , ΔT2-T1: -1.7±6.8mm, $p=0.6$) during the training period compared to usual care.

Conclusion: Functional power training improved isometric muscle strength and walking ability in children with SCP, without alterations in gastrocnemius medialis length. Enhanced motor control may play a significant role in the observed improvements in walking and running ability.

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ESTIMATING VO2 USING PERIPHERAL AND CENTRAL MEASUREMENTS OF WEARABLE SENSOR DATA

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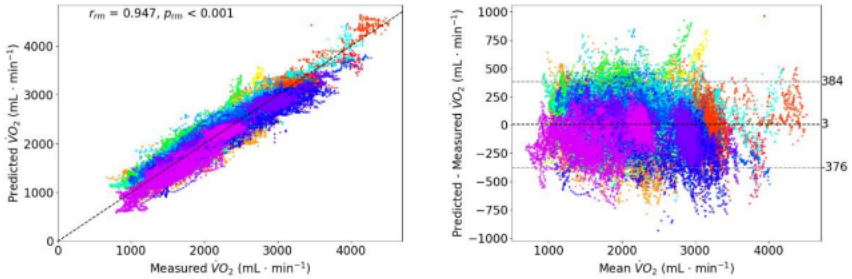
Introduction: Wearable sensors have been used to measure physiological data, however, their ability to estimate metrics of oxygen consumption ($\dot{V}O_2$) remains controversial. If wearable sensors could be employed alongside deep-learning methods to estimate $\dot{V}O_2$ and its kinetics, this would be widely applicable in research and applied settings.

Purpose: The purpose of this study was to: 1) validate the use of wearable sensors and deep-learning for predicting $\dot{V}O_2$ during variable-power output exercise; 2) assess the applicability of the Mean Normalized Gain (MNG) method for analyzing $\dot{V}O_2$ kinetics; and 3) investigate whether incorporation of near-infrared spectroscopy (NIRS) and body composition data could improve prediction accuracy.

Methods: 14 young, healthy participants (8 men, 6 women) performed a ramp-incremental exercise test and 3 pseudorandom binary sequence (PRBS) cycling protocols at varying intensities. $\dot{V}O_2$ was determined breath-by-breath using a COSMED Quark system, which served as ground-truth in the prediction models. A smart strap (Tymewear) was used to estimate heart rate and ventilation, NIRS was used to determine muscle oxygenation of the vastus lateralis, and bioelectrical impedance analysis was used for body composition. A Temporal Convolutional Network (TCN) was trained using leave-one-out cross-validation to predict $\dot{V}O_2$ from wearable data. Results were evaluated using repeated-measures correlation (r_{rm}) and Bland-Altman 95% Limits of Agreement (LoA).

Results: The TCN model predictions were strongly correlated with measured $\dot{V}O_2$ across all intensities (mean r_{rm} = 0.93; best-case r_{rm} = 0.94, $P < 0.001$). NIRS and BIA marginally strengthened these correlations (mean r_{rm} = 0.93; best-case r_{rm} = 0.95). However, the best-case Bland-Altman 95% LoA were wide (-0.38 L.min^{-1} to 0.38 L.min^{-1}), and the MNG between measured and predicted data were not correlated (r_{rm} = -0.16-0.45, P = 0.02-0.91).

Conclusions: This study demonstrates a good relative agreement between measured $\dot{V}O_2$ and that predicted from wearable data and deep learning. The addition of NIRS and BIA improved the accuracy of model predictions, however, the absolute agreement between measured and predicted data remained poor. Extraction of valid kinetic parameters from model predictions was also not possible. Whilst the initial results are promising, we expect that further refinements in data processing will serve to improve our model predictions.



A Repeated-measures correlation. Black dashed line represents line of identity.

B Repeated-measures Bland-Altman analysis. Black dashed line represents bias, grey dashed line represents 95% limits of agreement.

Figure 1: Best-case $\dot{V}O_2$ prediction results using all input data. Each colour represents a different participant.

AN INABILITY TO RECOVER: REDUCED SATELLITE CELLS IN PATIENTS WITH PEM

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Introduction: Patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and patients with long COVID are typically characterized by extreme fatigue and the worsening of symptoms with physical or mental exertion, known as post-exertional malaise (PEM). Patients with either ME/CFS or long COVID have been shown to have abnormal muscle histopathology, and often exhibit signs of muscular damage. It is well known that muscle satellite cell populations increase the ability for muscle to regenerate and repair following damage, and that with aging or inflammatory diseases the pool of viable satellite cells available diminishes. It is currently unknown whether patients with either ME/CFS or long COVID exhibit a similar abundance of satellite cells to healthy individuals.

Purpose: To investigate whether patients with ME/CFS and long COVID have a reduced number of satellite cells per myofiber, when expressed as a percentage of total myonuclear populations, which would suggest a decreased ability to repair and regenerate myofibers.

Methods: Biopsies were obtained from the vastus lateralis of 26 patients with ME/CFS, 25 patients with long COVID and 30 healthy age- and sex-matched controls 1-week before and 24-hours following exhaustive exercise. Biopsies were sectioned at 10um, and were stained with Pax7, DAPI, and wheat-germ albumin to visualize satellite cells, myonuclei, and myofiber membranes respectively. Satellite cell proportions are normalized to myonuclear count.

Results: Preliminary results show that patients with ME/CFS and long COVID have a reduced abundance of satellite cells at rest compared to healthy controls. The proportion of nuclei containing Pax7, however, was higher in patients compared to controls, suggestive of satellite cell activation at rest. Following exhaustive exercise, satellite cell abundance increased in all groups, while only patients increased in the proportion of nuclei expressing Pax7 signal.

Conclusion: Patients with ME/CFS or long COVID that experience PEM present with reduced satellite cell pools compared to healthy age- and sex- matched individuals, which ultimately may reduce their capacity to regenerate muscle following muscle damage. Additionally, an increase in satellite cell abundance and likely activation in response to exercise appears to be preserved, and may present a new avenue for therapeutics in patients experiencing PEM.

BODY COMPOSITION AND ENERGY EXPENDITURE OF PATIENTS WITH FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

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Introduction Fibrodysplasia Ossificans Progressiva (FOP) is an extremely rare bone disease leading to progressive immobilization due to the formation of heterotopic ossification (HO) in fibrous tissues. Compromised food intake, weight loss and anorexia are often seen in FOP patients, but implications of this disease on body composition and energy expenditure have not been investigated before.

Purpose In this study, we sought to gain insight in BMI, body composition and resting energy expenditure (REE) of FOP patients. These results were compared to calculated, patient-specific reference values and tested for correlation with disease severity.

Method We conducted a retrospective cohort study on thirteen FOP patients who underwent total body Dual-energy x-ray absorptiometry (DXA) scan. Data on body mass index, fat percentage and lean body weight (LBW) were extracted from the DXA scan and compared to reference values. In ten patients, further evaluation of REE and body composition was performed in a prospective observational study by indirect calorimetry and bio-electrical impedance. Disease severity was assessed by the CAJIS score, a scale to measure ankylosis of joints, and predicted REE was calculated with the WHO formula.

Figure 1. Measurement of REE using indirect calorimetry[1]

Results Data of seventeen different patients revealed six patients with low BMI (<18.5), of which four were severely underweight (BMI<17). Median BMI was lower in patients with a fully ankylosed jaw than in patients with no to moderate restricted mouth opening (16.0 vs. 23.3 kg/m^2, P=0.007). LBW was significantly lower in FOP patients compared to reference values (38.4 vs. 48.3 kg, P=0.033), while fat percentage was significantly higher (37.4% vs. 25.2%, P<0.001). Measured REE was lower than predicted in all patients (1211 vs. 1439 kcal/day, P=0.002) and measured REE as percentage of predicted REE was negatively correlated with CAJIS scores (Spearman r =-0.653, P=0.046).

Conclusion Underweight is prevalent in FOP patients, probably due to trismus leading to insufficient intake. Lower LBW and REE could be a result of loss of muscle mass following immobilization, which is supported by the negative correlation with disease severity. Further studies will address potential metabolic complications of sarcopenia, like insulin resistance, in these patients.

1. Created with BioRender.com

TIME- TIME-RESOLVED 3D-PC MRI MEASUREMENTS OF THE UPPER LEG MUSCLES DURING DYNAMIC KNEE FLEXION: THE EFFECT OF THE FATIGUE THRESHOLD

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Introduction: Many muscle diseases are marked by impaired muscle function, and the thighs are often earlier affected than the lower legs. Therefore, investigating thigh muscle function dynamically is highly important. Dynamic phase-contrast (PC) MRI is increasingly used to characterize muscle contractions. However, repetitive motion cycles are required, raising the risk of fatigue. Little is known about how exercising above and below the fatigue threshold (FT) affects PC-MRI data quality.

Purpose: This study aims to establish the fatigue threshold of hamstring muscles during knee-flexion exercise using multi-channel electromyography (EMG), and to examine the impact of performing repetitive exercise at intensities below and above the FT on the consistency of time-resolved 3D PC-MRI of the upper leg muscles.

Methods: Five healthy volunteers (34.4±9.4 years; 2 females) participated in this study, visiting the center twice. During the first visit, the FT of the right hamstrings was determined using EMG and a MR-compatible exercise device. Participants performed repetitive knee flexion, with resistance increasing every minute until failure. FT was identified as the deflection point on the EMG-force ratio graph. On the second visit MRI data were acquired in the right upper leg, including 3D Dixon and 3D-PC-MRI acquisitions at 90%FT and 110%FT to retrieve velocity information during exercise. Rate of perceived exertion (RPE) was assessed post trials.

Results: The FT was found at 30±8 % of the isometric force. RPE was significantly higher for the 110%FT condition than the 90%FT condition. Consistent temporal pattern was seen for the velocity values in feet-head (FH) direction during both FT conditions for all hamstring muscles. No differences were observed in the average muscle velocities in FH direction between conditions.

Conclusion: This study demonstrates the feasibility of determining a FT for the hamstring muscles during dynamic knee-flexion exercise. Despite the difference in perceived exertion, consistent motion patterns were found across both conditions. This suggests that exercising slightly above the FT threshold does not directly compromise velocity data. However, given that exercise above the threshold was perceived as heavy, further analyses are needed to investigate the effects of repeated contractions above the FT on strain, strain rate and their spatial distribution.

Modified Bone Mechanosensitivity in a PLS3 Knockout X-link Osteoporosis Mouse Model

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Purpose: Loss-of-function mutations in *PLS3* have been reported to cause X-linked osteoporosis and fractures but the molecular mechanism is still unknown. This study aims to set up a novel ubiquitous *Pls3* knockout (*Pls3* KO) mouse model to simulate PLS3 X-linked osteoporosis and better understand this disease.
Methods: A global *Pls3*^{em1cyagen} mouse model was generated in C57BL/6J mice, using the CRISPR/Cas 9 system at Cyagen Biosciences Inc. (China). Breeding, sacrificing, primers, allele names, and PCR conditions were applied as suggested by the manufacturer and animal ethics requirements. Axial loading was applied acutely (single bout) or repeated (5 loading cycles on 5 consecutive days) on the right tibia using a dynamic loading device: ElectroPlus E3000 (Instron). Custom-made cups are adapted to hold tibia on the loading device, 10 N as peak load and using 2Hz as the frequency with 10s rest period for 40 cycles one day. Bone tissues from hemizygous *Pls*3 KO mouse and wild-type littermates mouse (WT) were analyzed by 3-point bending test, microcomputed tomography (micro-CT) and bone histomorphometry.
Results: Pls3 gene expression was lower in all *Pls3* KO mouse compared to WT mouse. *Pls3* KO mouse tibiae presented a significantly lower breaking load and stiffness compared to their WT littermates. Micro-CT analysis indicated significant lower trabecular bone volume fraction, trabecular thickness, trabecular connectivity density and cortical thickness and a significantly higher trabecular separation (Tb.Sp) in Pls3 KO mouse. Acute axial loading of the mice tibiae resulted in an upregulation of the mechanosensitive genes: Cox2 and IL6 in WT mouse but not in *Pls3* KO mouse. Repeated loading in WT mouse showed a significant decrease in trabecular number (Tb.N) and a significant increase in Tb.Pf and trabecular structure model index (Tb.SMI). Repeated loading in *Pls3* mouse showed a different response: a significant increase in bone volume (BS/BV) and trabecular pattern factor(Tb.Pf) and a significant decrease in Tb.Sp and degree of anisotropy.
Conclusions: *Pls3* KO mouse showed an impaired bone microstructure and bone strength. Mechanical loading showed different effects in the *PLS3* KO mouse compared to the WT indicating the mechanosensitivity of the bone cells was affected, which may explain the osteoporosis and fractures.

The Impact of Exercise on Skeletal Muscle Integrity in Post-Viral Diseases: Investigating Myopathy in ME/CFS and Long COVID

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Introduction: Reduced exercise capacity and post-exertional malaise (PEM), characterized by illness following minimal physical exertion, are symptoms of post-viral diseases such as Long COVID (LC) and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Research using immunofluorescence microscopy and blood biomarkers suggests myopathic features, including immune cell infiltration, basal lamina thickening, impaired microvascular function, and mitochondrial dysfunction, contribute to its pathophysiology. However, current research lacks evidence on whether exercise exacerbates myopathic conditions and how basal lamina thickening relates to reduced exercise capacity and PEM. Therefore, the primary aim of this study is to assess changes in blood biomarkers associated with myopathy before and after exercise in LC and ME/CFS patients. The secondary aim is to investigate how basal lamina thickening is associated with reduced exercise capacity and PEM.

Methods: Vastus lateralis biopsies were collected from LC (N=25), ME/CFS (N=25), and healthy controls (N=25) prior to a maximal exercise test, during which cardiopulmonary exercise testing (CPET) and gas exchange threshold (GET) were assessed. Blood samples were taken before, one day post-, and one-week post-exercise, with fatigue levels assessed using questionnaires at each time point. Muscle biopsies were analyzed for Collagen IV and fiber cross-sectional area (FCSA) using immunohistochemistry. Blood biomarkers will be measured using Luminex assays.

Results: Muscle biopsies show increased amounts of Collagen IV in LC patients compared to ME/CFS ($p < 0.0001$) and controls ($p < 0.0001$), with ME/CFS patients also showing elevated levels compared to controls ($p < 0.0001$). Collagen IV deposition in LC associates with a lower FCSA ($R^2 = 0.250$, $p < 0.01$) and GET ($R^2 = 0.214$, $p < 0.05$). Biomarkers of endothelial dysfunction, muscle injury, and immune dysregulation are expected to be elevated in both LC and ME/CFS compared to controls, with further increases observed post-exercise relative to baseline.

Conclusion: Increased Collagen IV and anticipated biomarker elevations suggest a form of myopathy in LC and ME/CFS patients. The relationship between Collagen IV deposition, FCSA, and GET in LC may indicate a fibrotic-like phenotype contributing to the symptoms also present in ME/CFS. Additionally, the suspected biomarker elevations one day and one-week post-PEM induction suggest a detrimental effect of exercise in ME/CFS and LC.

COATING 3D-PRINTED BIOCERAMICS WITH HISTATIN PROMOTES ADHESION AND OSTEOGENESIS OF STEM CELLS

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Abstract

Introduction: Mesenchymal stem cell and 3D printing-based bone tissue engineering are promising techniques to repair large-volume bone defects. The success of this technique is highly dependent on the activities of stem cells such as cell attachment, spreading, osteogenic differentiation, and *in-vivo* survival on 3D printed scaffolds. **Purpose**: In this study, we wished to develop a cell-targeting strategy and explore its application potential in promoting the interaction between MSCs and 3D printed scaffolds for bone tissue engineering. **Method:** We adopted histatin-1 (Hst1) to enhance the interactions of human adipose-derived stem cells (hASCs) on 3D printed β-tricalcium phosphate (β-TCP) scaffolds. we first assessed the time-course and dose-dependent effects of Hst1 on the adhesion and spreading of hASCs on 3D printed β-TCP scaffolds to select the optimal condition of Hst1. Thereafter, we investigated Hst1's effects on the proliferation, osteogenic differentiation, and *in-vivo* survival of hASCs on β-TCP scaffolds. We also adopted specific inhibitors to explore the potentially involved signaling pathways. **Results**: Fluorescent images showed that Hst1 significantly enhanced the total numbers and surface area of hASCs on both bio-inert glass and 3D printed β-TCP scaffold. In addition, Hst1 was associated with significantly higher proliferation, alkaline phosphate staining on 3D printed β-TCP scaffolds than the control. Subsequently, the small animal imaging showed that the fluorescent densities of the Hst1-treated hASC/3D printed TCP construct were always significantly higher than those of the control. The specific inhibitors of ERK and p38 but not JNK signaling significantly inhibited the adhesion of hASCs. Hst1 promoted total fluorescent intensities of talin, vinculin, and paxillin per cell. **Conclusion**: Hst1 could significantly promote the adhesion, spreading, osteogenic differentiation, and in vivo survival of hASCs on 3D-printed β-TCP scaffolds, bearing a promising application in stem cell/3D printing-based constructs for bone tissue engineering.

Static skeletal muscle exosomes inhibit osteogenic differentiation of BMSCs via the miRNA6363/S100A8 axis

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Abstract

Introduction: Limited activity of orofacial muscles is one of the primary causes of maxillofacial developmental disorders in children, induced by Orofacial Myofunctional Disorder (OMD). Exosomes, which are rich in proteins and nucleic acids, play a crucial role in muscle-bone crosstalk. Preliminary experimental results indicate that Static skeletal muscle exosomes (Ssm-Exos) can inhibit the osteogenic differentiation of Bone Marrow Stromal Cells (BMSCs). Hence, we propose the scientific question: What is the mechanism by which Ssm-Exos inhibit BMSC osteogenic differentiation? **Purpose**: We aim to clarify the inhibition mechanism of Ssm-Exos on BMSC osteogenic differentiation through the miRNA/key gene axis. **Methods:** 1. Exosome extraction via differential centrifugation and identification using TEM, nano-flow cytometry, and western blotting. 2. Analysis of the effect of exosomes on BMSC osteogenic differentiation using RT-qPCR, ALP staining, and Alizarin Red staining(ARS). 3. Identification of key inhibitory genes (S100A8) and verification of miRNA6363 enrichment in Ssm-Exos through high-throughput sequencing, miRNA detection, and dual-luciferase assays. 4. Overexpression of S100A8 in BMSCs, with subsequent analysis of BMSC osteogenic differentiation, S100A8 expression and intracellular calcium ion levels. **Results**: Ssm-Exos were isolated and characterized. Ssm-Exos inhibited osteogenic differentiation of BMSCs by RT-qPCR and ARS. High-throughput sequencing results showed that S100 calcium binding protein A8(S100A8), was robustly downregulated in Ssm-Exos-treated BMSCs. Downregulated S100A8 decrease intracellular Ca^{2+} concentration and inhibited osteogenic differentiation of Ssm-Exos -treated BMSCs. The overexpression of S100A8 in BMSCs rescued Ssm-Exos-inhibited osteogenic differentiation. Furthermore, our experimental results demonstrated that miRNA6363 is significantly enriched in Ssm-Exos and can bind to S100A8, thereby inhibiting its expression. **Conclusion**: *In vitro* experiments show that Ssm-Exos reduce S100A8 expression in BMSCs through miRNA6363, decrease intracellular Ca^{2+} concentration, and inhibit BMSC osteogenic differentiation. This study is the first to report that static skeletal muscle can inhibit BMSC osteogenic differentiation through the miRNA6363/S100A8 axis. It provides new insights into the mechanisms underlying OMD-induced maxillofacial developmental disorders and offers potential new therapeutic targets.

[^{18}F]NaF PET/CT AS A MARKER FOR FIBRODYSPLASIA OSSIFICANS PROGRESSIVA: FROM MOLECULAR MECHANISMS TO CLINICAL APPLICATIONS IN BONE DISORDERS

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Introduction: Fibrodysplasia ossificans progressiva (FOP) is a rare genetic bone disorder characterized by episodic flare-ups in connective tissue, which are frequently followed by the formation of heterotopic ossification. The absence of available plasma-soluble biomarkers for flare-ups or heterotopic bone formation poses severe challenges to the monitoring of disease activity to measure or predict disease progression. Recently, 18-fluor-sodium fluoride positron emission tomography/computed tomography ([^{18}F]NaF PET/CT) was introduced as a potential marker for ossifying FOP activity.

Purpose: With this review, we aim to provide an overview of [^{18}F]NaF PET applications related to bone disorders, with special focus on the use of [^{18}F]NaF PET as a marker for bone metabolism in FOP.

Methods: A review of all relevant papers on [^{18}F]NaF PET/CT use for FOP known to the authors was conducted.

Results: This review discusses the pharmacokinetics of [^{18}F]NaF in relation to the pathophysiology of FOP, and its use as a marker of local bone metabolism in a variety of bone-related disorders.

Conclusion: At present, [^{18}F]NaF PET/CT is the only available biological marker for HO formation in FOP, but additional research is required to further specify the relation between tracer uptake and disease activity, and to establish a standardized approach for [^{18}F]NaF PET/CT interpretation.

EXERCISE-INDUCED TRANSLOCATION OF GLUT4 TOWARDS THE MITOCHONDRIA AND T-TUBULES IN SKELETAL MUSCLES OF PATIENTS WITH TYPE I DIABETES MELLITUS

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Introduction Glucose transporter 4 (GLUT4) is a protein facilitating the transport of glucose into muscle and fat cells. GLUT4 translocation is induced either via an insulin-dependent pathway or an insulin-independent pathway activated by skeletal muscle contractions. Exercise is an important therapeutic approach for type I diabetes mellitus (T1DM) patients that enhances muscle glucose uptake, however, they often experience post-exercise hypoglycemia. In onder to gain insight into hypoglycemia, we study the translocation of GLUT4 to organelles associated with glucose metabolism such as transverse tubules (T-tubules) and mitochondria in both healthy and T1DM individuals.

Purpose This study aim to analyze specific cellular locations where GLUT4 transporters translocate to before and after exercise both in T1DM and healthy individuals. GLUT4 translocation studies would provide a better understanting of exercise-stimulated glucose metabolism.

Methods Immunohistochemical staining, confocal and widefield microscopy were used to analyze the *vastus lateralis* muscle biopsies taken from the healthy controls (n=11, HbA1c=5.05±0.22%) and T1DM patients (n=18, HbA1c=6.38±0.67%) before and after 30-minute bout of moderate intensity exercise. There were no significant differences between the two groups in terms of sex, age, BMI etc. except for their glucose control. Biopsy sections were stained with fluorescent probes specific for GLUT4, mitochondria, T-tubules and cell-membrane (Figure 1). Microscopy images were deconvolved and examined using different analytical tools (Manders' and Pearson's coefficients) to evaluate GLUT4 co-occurrence and colocalization with mitochondria and T-tubules.

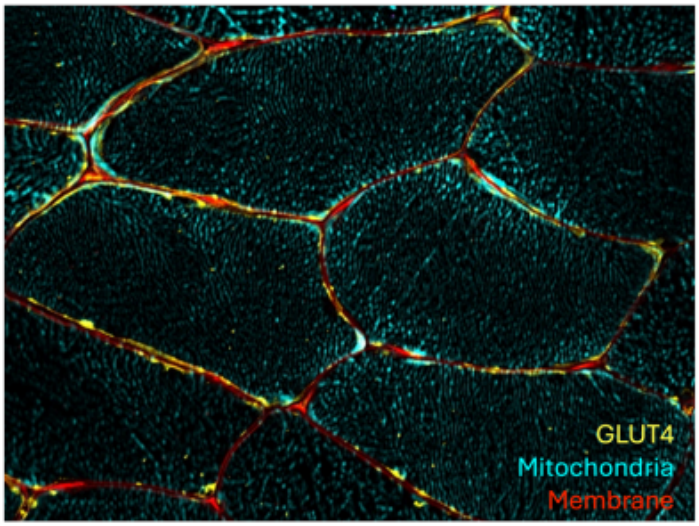

Figure 1. Typical example of GLUT4 staining.

Results Preliminary results show, that GLUT4 translocation towards the mitochondria is increased in healthy individuals compared to the T1DM (Pearson's, healthy 0.17±0.04 *versus* T1DM 0.12±0.05, p=0.04). This indicates, that GLUT4 translocate not only towards the membrane but specifically towards the subsarcolemmal and paravascular mitochondria in both groups before and after the exercise, with an induced translocation in healthy controls.

Conclusion These findings suggest, that GLUT4 translocation towards the mitochondria might be disturbed in T1DM. Differences in GLUT4 translocation in healthy and T1DM individuals could offer new potential therapeutic strategies for T1DM patients, ways to prevent post-exercise hypoglycemia and provide a better insight into skeletal muscle glucose metabolism.

Nicotinamide riboside supplementation prevents the onset mitochondrial dysfunction in a mouse model for nemaline myopathy type 6

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Nemaline Myopathy type 6 (NEM6) is caused by variants in Kelch-repeat-and-BTB-(POZ)-Domain-Containing-13 (*KBTBD13*). The majority of the NEM6 patients harbors the Dutch founder mutation *KBTBD13*^{R408C} (c.1222C>T, p.Arg408Cys) resulting is a hypercontractile phenotype caused by sarcomere-based impaired muscle relaxation. Histological characterization of NEM6 patient biopsies by NADH staining show the presence of cores, indicating the absence of complex I (NADH) activity suggesting mitochondrial dysfunction.

In this study we aim to perform a natural history study to investigate whether hypercontractility contributes to mitochondrial dysfunction in NEM6, using homozygous *Kbtbd13*^{R408C}-knockin mice (NEM6 mouse model). First, enzymatic NADH staining showed absence of cores at 1 month, onset at 3 and progression of cores at 9 months. Therefore we can conclude that the NEM6 mouse model phenocopies the mitochondrial abnormalities in NEM6 patients. Second, mitochondrial respiration was investigated by *in vitro* high-resolution respirometry. In line with the presence of NADH cores at 3 and 9 months old, soleus muscle of NEM6 mice showed significant decreased total OXPHOS and NADH-linked respiration. To study the functional consequences in vivo, metabolic treadmill experiments were performed. These experiments showed significant impaired running performance, decreased VO_2max and increased respiratory exchange ratio (RER) in NEM6 mice. To study the pathways underlying mitochondrial dysfunction in NEM6 muscle, metabolomics and proteomics were performed on soleus muscle. Joint pathway analysis revealed alterations in TCA cycle related metabolites and proteins in NEM6 mice. Of special interest, NAD^+ levels in 3 and 9 months old NEM6 mice were significantly decreased. We attempted to prevent the onset of the mitochondrial phenotype with supplementation of nicotinamide ribose (NR), a NAD^+ precursor that is generally considered safe and is currently in many clinical trials. One month old WT and NEM6 mice received nicotinamide riboside (NR) supplementation for 8 weeks. Our data showed that chronic NR supplementation prevent the onset of both total OXPHOS and NADH-linked respiration in NEM6 mice. To conclude, this study provided insights into the natural history of mitochondrial dysfunction in NEM6 and provides proof-of-concept for the ability of NR to revert the mitochondrial phenotype in NEM6.

THE ROLE OF EXERCISE-INDUCED MECHANICAL LOADINGS ON MACROPHAGE ACTIVATION IN MUSCLE REGENERATION: A BIOINFORMATICS ANALYSIS

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Introduction Skeletal muscle injuries constitute a significant portion of sports-related trauma and are also prevalent in chronic muscle diseases. These injuries can severely impact daily activities and overall quality of life. Early mobilization or exercise has been shown to promote regeneration and was recommended for accelerating recovery. The innate immune system plays a pivotal role in muscle regeneration by coordinating inflammatory and repair phases through macrophage activation and polarization. It is highly conceivable that exercise-induced mechanical loadings affect macrophage function within the muscle tissue and the communication with neighboring cells, including muscle stem cells. However, whether the activation of macrophages can be triggered independently by exercise-related mechanical loadings, except from damage signaling remains unclear. Additionally, the paracrine effect of mechanically activated macrophages on muscle stem cell activity or muscle regeneration post-exercise is yet to be fully elucidated.

Purpose To explore how exercise-induced mechanical loadings affect macrophage activation, cytokine expression patterns, functional responses, and cell-cell interactions based on transcriptomic data.

Methods We used a publicly available transcriptomic dataset (GSE214544) from a study in which three healthy, moderately active individuals performed three 30-second all-out sprint exercises[1]. Data analysis was conducted using R. A t-SNE algorithm was applied for the reduction and cell annotation. After identifying the DEGs, a GO and GSVA enrichment analysis was performed. A Monocle package was used for pseudotime analysis, and a Cellchat package was used to evaluate the cell-cell interactions.

Results The analysis revealed significant enrichment of immune and inflammatory pathways post-exercise, with an increased M1/M2 macrophage ratio. Exercise also led to a fourfold increase in both the number and strength of interactions between neighboring cells. Notably, **the interaction between M1 macrophages and satellite cells was predominantly mediated by the Epiregulin (EREG)–Epidermal Growth Factor Receptor (EGFR) pathway, with EREG showing a Log2 fold change (>2) following exercise.**

Conclusions: Acute exercise activates immune and phagocytic processes within the knee extensor muscles, driving macrophage polarization towards the M1 phenotype and upregulating pro-inflammatory and growth factor-related gene expression. A striking finding was the substantial upregulation of the EREG/EGFR signaling pathway, which exhibited the highest interaction probability between M1 macrophages and satellite cells. Given that epiregulin is a potent stimulator of cell proliferation, its increased expression following exercise may underlie the beneficial effects of exercise on muscle regeneration.

[1]Lovrić A ea Commun Biol. 2022:5(1):1121

Impaired muscle fiber contraction in patients and reduced murine muscle fiber contractility after human serum exposure in IMNM

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Background:
Immune-mediated necrotizing myopathy (IMNM) is the most severe myositis subtype in terms of muscle weakness. Immunosuppressive therapies are still insufficient and there is a need for better and personalized therapies. IMNM is also associated with myositis specific autoantibodies (MSAs) against signal recognition protein-54 (SRP) and 3-hydroxy-3-methylglutaryl CoA reductase (HMGCR), which have been suggested to play a pathogenic role. To date, the muscle weakness has been ascribed to necrosis, but the proportion of necrotic fibers is too low to account for the clinical muscle weakness. This raises the question whether impaired fiber contractility plays a role and whether this is caused by MSAs.
Methods:
A muscle biopsy was obtained from treatment naieve IMNM patients with anti-SRP^{+} patients (N=6), anti-HMGCR^{+} patients (N=7) and from healthy controls (N=12). Single skeletal muscle fibers were mechanically dissected from the corresponding glycerinated biopsy. Fibers were clipped, permeabilized and mounted between a force transducer and a length motor. Fibers were moved between baths with solutions containing incremental [Ca^{2+}]. Furthermore, we have developed an *ex vivo* murine muscle fiber culture model, in which contractility and calcium handling are measured by an innovative high throughput setup. It allows us to test the effects of serum and total IgG from anti-SRP^{+} (N=5), anti-HMGCR^{+} (N=5) and seronegative (N=5) patients on cell survival and muscle fiber contractility during electrical stimulation.
Results:
First, our data show a significant decrease in the maximum, normalized (to fiber cross sectional area) force generating capacity in human muscle fibers from both MSA groups, indicating impaired sarcomere contractility. The data also show a reduced calcium sensitivity of force, i.e. more calcium is needed to produce a given submaximal level of force in the anti-SRP^{+} patients. Second, our data show a lower survival in healthy murine muscle fibers during continuous exposure to anti-SRP^{+}, anti-HMGCR^{+} and seronegative serum. Third, our data show a significant increase in sarcomere shortening after exposure to patient serum.
Conclusions:
These data suggest that the reduced muscle weakness in IMNM patients not only results from necrotic fibers, but also from sarcomere dysfunction. Our murine high throughput model shows a lower survival during continuous exposure to patient serum and an increase in sarcomere shortening after exposure patient serum.

2. Clinical Sciences

EXPERIENCES WITH HOSPITAL-TO-HOME TRANSITIONS: PERSPECTIVES FROM PATIENTS, FAMILY MEMBERS AND HEALTHCARE PROFESSIONALS. A SYSTEMATIC REVIEW AND META-SYNTHESIS OF QUALITATIVE STUDIES

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**Juul van Grootel and Romain Collet contributed equally to the paper*

Abstract

Introduction

Over the years, global healthcare has changed due to the aging of the population and the increasing prevalence of multimorbidity. Transitional care interventions have been developed to ensure the coordination and continuity of care across various locations or levels of care. Multiple studies have explored the needs and experiences of patients, family members, and healthcare professionals regarding these hospital-to-home transitions. Conducting a meta-synthesis of qualitative studies on this topic can provide a comprehensive overview and understanding of patient and (allied) health professional needs regarding this sensitive moment in the recovery phase after hospital admission.

Purpose Our study aimed to identify, critically appraise, and summarize studies investigating experiences with transitional care in a qualitative meta-synthesis. To form a basis for the development of a transitional integrated allied healthcare pathway for patients with complex care needs after hospital discharge.

Methods Medline, CINAHL and Embase were systematically searched to identify eligible articles from inception to June 2024. Qualitative studies were included and critically appraised using the Critical Appraisal Skills Program. Insufficient-quality papers were excluded. We performed a meta-synthesis following 1) open coding by two independent researchers and 2) discussing codes during reflexivity meetings.

Results

Ninety-eight studies were appraised, of which 53 were included. We reached thematic saturation, four themes were constructed: 1) care coordination and continuity, 2) communication, 3) patient and family involvement, and 4) individualized support and information exchange. For patients and families, tailored information and support are prerequisites for a seamless transition and an optimal recovery trajectory after hospital discharge. It is imperative that healthcare professionals communicate effectively within and across care settings to ensure multidisciplinary collaboration and care continuity.

Conclusions

This study identifies essential elements of optimal transitional care. These findings could be supportive to researchers and healthcare professionals when (re)designing transitional care interventions to ensure care continuity after hospital discharge.

SOCIETAL COSTS OF OLDER ADULTS WITH LOW BACK PAIN SEEKING CHIROPRACTIC CARE: FINDINGS FROM THE BACE-C COHORT STUDY

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Introduction
Low back pain (LBP) is a major cause of sickness absence, work disability and reduced productivity, and is therefore associated with significant costs for individuals and society.
Older people with LBP might have different cost-patterns in comparison to younger people with LBP (e.g. due to their retirement and/or co-morbidities). Therefore, it is important to identify the possible risk factors for high costs in older adults with LBP.

Purpose
To describe the societal costs during one year of follow-up among older adults seeking chiropractic care due to a new episode of LBP, and to determine what factors predict high societal costs in this population.

Method
A prospective cohort study of 223 participants, ≥ 55 years of age with a new episode of LBP seeking chiropractic care in chiropractic private practices in the Netherlands (n=38) with total societal costs as the primary outcome (costs in the top 20th percentile). The final prediction models were obtained using forward selection. The model's prognostic accuracy and discriminative ability were assessed, and the models were internally validated using bootstrapping.

Results
The mean total annual societal cost per patient was €5297 (95% CI 4191–6403), with presenteeism as the biggest cost driver (65% of total costs). Costs were higher among non-retired participants (€7759; 95% CI 6047–9470) than retired participants (€1892; 95% CI 1088–2695). In the total population, younger age, being male, lower alcohol intake, working instead of retirement, and more disability at baseline were found to be predictive of high societal costs. Working was found to be the strongest predictor of high societal costs. The model's fit was good, its explained variance was moderate (28%) and their AUCs could be interpreted as moderate (0.85).

Conclusion
This study estimated the mean total annual societal cost of older adults seeking chiropractic care due to a new episode of LBP at €5297 (95% CI 4191–6403). These costs were mainly due to high levels of presenteeism and extensively differed based on work status.

Long-Term Follow-Up After Rotationplasty: Good functional results despite osteoarthritis and pain in (pseudo)knee

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Background

Rotationplasty is a surgical procedure for patients with malignancies around the knee or congenital femoral defects. Altered biomechanics from gait deviations may increase the risk of osteoarthritis in the lower extremities. This study aims to evaluate osteoarthritis development in the (pseudo)knee (rotationplasty ankle), contralateral ankle and both hips, alongside its impact on pain and daily functioning.

Method

Survivors after rotationplasty between 1980-2002 at the Amsterdam University Medical Centers were invited to participate (n=35); 30 agreed. Radiographs of both hips, the (pseudo) knee, and contralateral ankle were analyzed for osteoarthritis using the Kellgren-Lawrence grading system, focusing on osteophytes and joint space narrowing. Functional outcomes, pain, quality of life and sports participation were assessed using Harris Hip Score, FAOS, and AOFAS questionnaires. Statistical analyses included one-sample t-tests and correlations between OA findings and BMI, age, and questionnaire results.

Results

Thirty patients, median age 47 years (IQR 43-51) with a median follow-up of 33 years (IQR 29-35), participated. Moderate-to-definite osteoarthritis was identified in 35% of ipsilateral hips versus 11% contralaterally and in 43% of ipsilateral (pseudo)knees versus 10% in the contralateral ankle. Osteophytes and joint space narrowing were prevalent in medial and subtalar regions. Functional outcomes showed preserved hip function, with good pain and alignment scores on FAOS and AOFAS. However, sports participation and quality-of-life were reduced. Osteoarthritis significantly correlated with pain in the ipsilateral ankle and Harris-Hip Score for the contralateral hips.

Conclusion

High osteoarthritis rates were observed in ipsilateral hips and (pseudo)knee. Despite the radiographic presence of OA, functional outcomes were largely preserved. Although, pain associated with osteoarthritis in the (pseudo)knee highlights the long-term consequences of this procedure.

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COMPARING THE EFFECTIVENESS OF TRADITIONAL TEACHING METHODS WITH MULTISENSORY TEACHING METHODS (3D MODELS) IN TEACHING THE YOUNG AND BURGESS CLASSIFICATION OF PELVIC RING FRACTURES

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Introduction Pelvic ring fractures are a critical focus in trauma care, with the Young & Burgess classification serving as a pivotal framework for understanding injury mechanisms and determining treatment strategies. The complexity of this classification poses challenges for medical students, necessitating innovative teaching approaches.

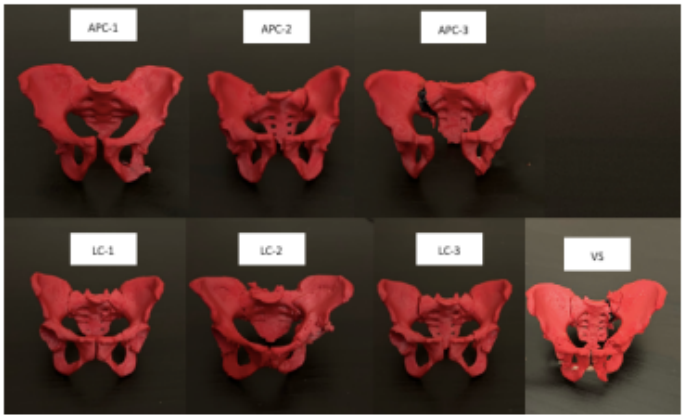

Figure 1: 3D-models of pelvic ring fractures

Purpose This study evaluates the effectiveness of multisensory teaching methods, incorporating 3D-printed fracture models **(fig.1)**, compared to traditional teaching methods.

Method A prospective study was conducted with 56 fourth-year medical students from two universities in Amsterdam. Participants were divided into a control group (n=39) and an intervention group (n=17). The control group attended a traditional lecture using textual and visual materials. The intervention group participated in an additional hands-on session with 3D-printed pelvic ring fracture models. Four days post-intervention, students completed a digital quiz assessing comprehension and classification accuracy of pelvic fractures. The primary outcome was classification accuracy; secondary outcomes included identifying challenging aspects of the classification system. Statistical analysis involved independent T-tests.

Results The intervention group performed significantly better, with a mean score of 53.65% compared to 40.46% in the control group (p=0.045). No significant differences were observed for APC and LC fractures. However, a significant difference was found for VS fractures, with the control group scoring 30.8% and the intervention group scoring 70.6% (p <0.001).

Assessment scores on Pelvic Ring Fracture Classification Understanding

	M (Score %)		Significance	
	Control group (n=39)	Intervention group (n=17)	*P*-value	95% BI
Overall score	40,46	53,65	0.045	[-26.1, -0.3]
Score by pelvic fracture subtype				
APC	57,69	64,71	0.443	[-25.2, 11.2]
LC	30.77	37,65	0.340	[-21.2, 7.4]
VS	30.77	70,59	<0.001	[-59.8, -19.9]

Conclusion This study suggests the use of 3D models significantly enhanced students' understanding and ability to classify pelvic ring fractures using the Young & Burgess classification system compared to traditional methods. This approach shows promise for improving trauma education quality.

THE CORRELATION BETWEEN MENTAL HEALTH STATUS AND CLINICAL OUTCOMES IN PATIENTS WITH OSTEOCHONDRAL LESIONS OF THE TALUS

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Introduction

Mental health and pain are closely but intricately connected, and negative psychological constructs are associated with foot and ankle pain and poorer postoperative outcomes after orthopedic surgery. This relationship between mental health and pain may play a role in patients with osteochondral lesions of the talus (OLT), given the complex clinical presentation of these patients.

Purpose

This study aimed to investigate the correlation between pre-treatment mental health and the Foot and Ankle Score (FAOS) pain subscale at 2-year follow-up in patients with OLT.

Method

This retrospective analysis of prospectively followed patients investigated patients with a symptomatic OLT, who were 16 years and older and had undergone any treatment for an OLT between January 2018 and November 2024. Mental health was assessed using the Mental health Inventory-5 (MHI-5) subscale of the SF-36. The primary outcome was the FAOS pain subscale. Secondarily, the correlation between the SF-36 Mental Component Scale (MCS) and FAOS QoL at baseline and FAOS pain at follow-ups has been investigated. A multivariate regression model was used to assess the correlation between these mental health questionnaires and FAOS pain at 1-year and 2-year follow-up, with mental health stratified into quartiles.

Results

319 patients were included at baseline, of which 216 patients reached 1-year follow-up, and 176 2-year follow-up. No differences in FAOS pain at 1- and 2-year follow-up were found between quartiles for the MHI-5 and MCS. Patients in the lowest FAOS QoL quarter had a lower FAOS pain score at 1-year (β = -11,52 [95% CI -19,26 to -3,78], p = <0,01) and 2-year follow-up (β -11,10 [95% CI -20,70 to -1,50] p = 0,02).

Conclusion

There was no difference in FAOS pain scores at 1- and 2-year follow-up across MHI-5 and MCS quartiles for patients with OLT. However, patients in the lowest FAOS QoL quartile at baseline reported significantly higher FAOS pain at both follow-ups, suggesting an impact of psychological constructs on clinical outcomes in patients with OLT.

DEVELOPMENT OF THE DANCE MENTAL HEALTH ASSESSMENT TOOL

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Introduction: The prevalence of mental health disorders in professional ballet dancers is high, and care remains difficult given the lack of screening tools. A mental health assessment tool is needed to screen dancers and act in case of mental health symptoms. Such a tool has been developed for athletes (Sport Mental Health Assessment Tool 1 (SMHAT-1)). Because dancers' context and mental health issues profile differ from that of elite athletes, it is necessary to adapt the SMHAT-1.

Purpose: The aim of this study was to develop a Dance Mental Health Assessment Tool (DMHAT-1) to screen for mental health symptoms in professional dancers.

Methods: The Intervention Mapping and Knowledge Transfer Scheme guided the development. A narrative review of the assessment tools for psychological stressors and mental health symptoms in dancers was conducted. Following the review, a group of experts on mental health and professional dancers' health was formed to provide their opinions on the changes needed to develop the DMHAT-1.

Results: To develop the DMHAT-1, we adapted the content of the SMHAT-1 based on a narrative review and expert input. The DMHAT-1 includes three dancer forms, starting with the triage form. This form combines a modified version of the Athlete Psychological Strain Questionnaire, a list of psychological symptoms, and questions about mental health professional consultations. Dancers scoring above a cut-off (to be determined in the validation study) must complete Dancer's Form 2, which includes validated questionnaires on anxiety, depression, sleep disorders, alcohol/drug use, and eating disorders. If any questionnaires exceed the established cut-off, Dancer's Form 3 should be completed, covering attention deficit/hyperactivity disorder, mood disorders, post-traumatic stress disorder, gambling, and psychosis risk. If no questionnaire scores exceed the cut-off, dancers should continue to be monitored with the triage tool. Dancers reporting suicidal thoughts should be urgently referred to a psychologist or psychiatrist.

Conclusion: The DMHAT-1 was developed to screen mental health symptoms in professional dancers and to identify individuals who might need further mental health assistance. Future research will focus on assessing its validity and reliability.

FEASIBILITY AND USABILITY OF A CLINICAL DECISION SUPPORT SYSTEM FOR TREAT-TO-TARGET IN SYSTEMIC LUPUS ERYTHEMATOSUS: *THE T2T-SLE PILOT STUDY*

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Introduction: The Treat-to-Target (T2T) strategy is endorsed for systemic lupus erythematosus (SLE) management, yet its implementation remains challenging[1]. A clinical decision support system (CDSS) was developed to assist physicians in applying a T2T approach in clinical practice[2].

Purpose: This study assessed the feasibility, usability, and acceptability of a CDSS for T2T-based SLE management from physicians and patient perspective.

Methods: The T2T-SLE study was a 24-week, non-randomized, cluster, multicenter pilot study conducted in North Holland, including two tertiary university medical centers (UMCs) and two regional outpatient clinics. Patients diagnosed with SLE were assigned by treatment center to either routine care or T2T-CDSS-assisted care. The CDSS, developed based on evidence-based guidelines, provided clinical recommendations for disease management. Primary outcomes included feasibility (recruitment, retention, and implementation challenges), usability (physicians perceived ease of use of the CDSS web-app), and acceptability (physician and patient satisfaction). The CDSS was evaluated solely by physicians, with one physician in a UMC and one in a regional center using the tool. In turn, patients reported their satisfaction with the T2T strategy, which involved more frequent visits and structured discussions on treatment targets. Patient feedback was collected through qualitative questionnaires and patient-reported outcome measures (PROMs). Secondary outcomes included treatment patterns, disease activity measures, and implementation barriers and facilitators.

Results: Of 91 screened participants, 38 were enrolled (41.8%) and 35 completed the study (92.1% retention). The most common reason for declining participation was lack of interest (23.1%) followed by unspecified reasons (24.7%) and scheduling conflicts due to life events (4.4%). (Fig. 1). The enrolled population was representative of a broad spectrum of SLE severity. Patients in the T2T-CDSS group had slightly lower baseline disease activity scores compared to the routine care, though both groups exhibited similar demographic characteristics (Table 1). Physicians reported that the CDSS was useful in supporting T2T-based decision-making, but challenges related to workflow integration and time constraints were noted. Patients in the T2T group generally expressed satisfaction with the strategy, valued increased monitoring and structured discussions but had some concerns about the burden of more frequent visits.

Conclusions: The T2T-SLE study demonstrated the feasibility of using a CDSS for T2T implementation in SLE management. Physician-reported usability was positive, though workflow integration challenges were noted. Patients valued structured treatment discussions but reported mixed opinions on visit frequency. The study demonstrated feasibility for larger-scale implementation, though recruitment delays and engagement challenges indicate a need for improved patient outreach strategies. Future studies should optimize recruitment strategies and further assess long-term clinical effectiveness.

[1]Parra Sánchez AR, ea Nat Rev Rheumatol. 2022 doi: 10.1038/s41584-021-00739-3.

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Fig 1. ***Enrollment Diagram, Inclusion and Exclusion Criteria***

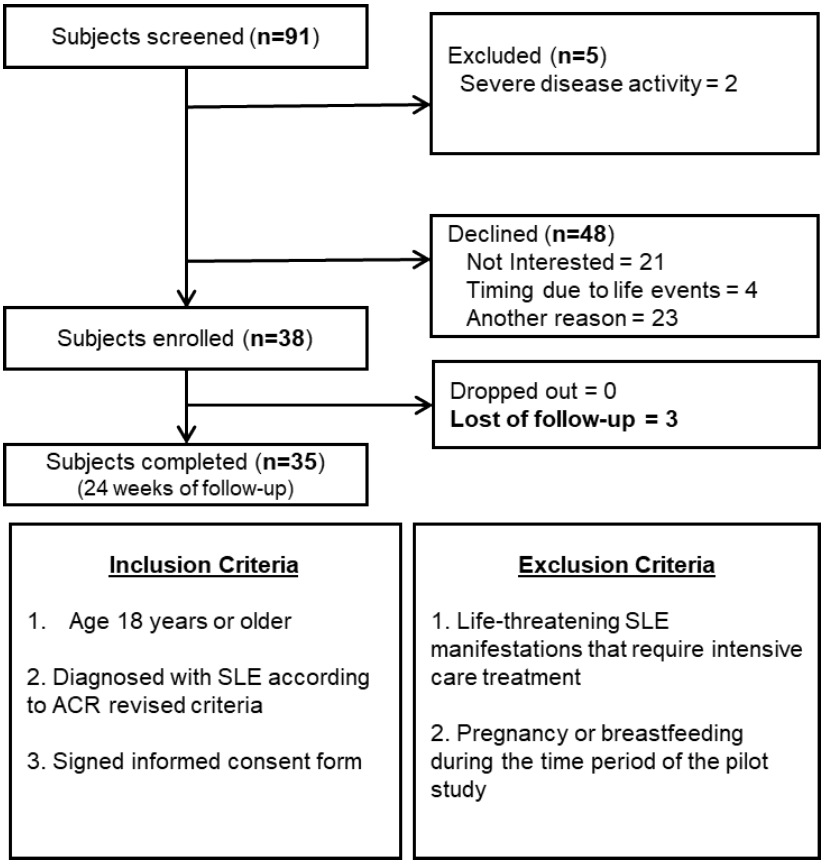

Table 1. Baseline characteristics in patients from the treat-to-target and the routine care group

	Treat to target group (n=18)	Routine care group (n=17)
Age, mean (S.D.)	40.2 (11.9)	46.8 (8.7)
Female gender, n (%)	16 (88.8)	16 (94)
Caucasian ethnicity (%)	14 (77.7)	14 (82.3)
Disease activity measures:		
SLEDAI-2K, (median (IQR))	2 (1-6)	2 (0-5)
cSLEDAI-2K, (median (IQR))	1 (0-2)	0 (0-4)
PGA (0-3), (median (IQR))	0.65 (0.3-1.4)	0.4 (0.3-0.6)
SLICC/ACR damage index, (median (IQR))	1 (0-2)	1 (0-4)
Treatment variables:		
Glucocorticoids, n (%)	9 (50)	11 (64.7)
Antimalarials, n (%)	16 (88.8)	17 (100)
Immunosuppressants, n (%)	10 (55.5)	8 (47)
Biologics, n (%)	2 (11)	0 (0)
PROMs:		
PaGA (0-10), (median (IQR))	3 (1-7)	4.5 (2-7)
FACIT score, (median (IQR))	26 (17-42)	33 (31-47)
SF-36		
PCS, mean (S.D.)	41.2 (12.7)	44.5 (11.1)
MCS, mean (S.D.)	50.3 (10.8)	48.1 (12.3)

FEASIBILITY AND VALIDITY OF THE ADJUST-AFO FOR OPTIMIZING ANKLE-FOOT-ORTHOSES STIFFNESS IN PATIENTS WITH CALF MUSCLE WEAKNESS

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Introduction

Spring like ankle-foot-orthoses (AFOs) enhance walking in individuals with calf muscle weakness by reducing gait deviations[1,2,3]. The effectiveness of AFO's depends on optimizing the bending stiffness[4]. Which is currently done by manually changing the stiffness, followed by measuring gait biomechanics and energy cost for each stiffness, which is time-consuming and burdensome for patients. The ADJUST-AFO was developed to speed-up the optimization process by enabling a 20 minute continuous measurement due to adjustable stiffness during walking[5]. Its feasibility and validity compared to the manual procedure needs to be determined.

Purpose

Is the ADJUST-AFO a feasible and valid tool to optimize the AFO bending stiffness in individuals with calf muscle weakness compared to manual optimization?

Method

Six patients with non-spastic calf muscle weakness are included (4 males, mean age: 68.1 ± 2.94 years). Participants underwent 3D gait analysis and energy cost (EC) tests at a self-selected speed with five stiffness settings (2.8-6.6 Nm/degree) with the manual procedure and the ADJUST-AFO procedure, with two weeks in between. To ascertain feasibility, completion of the measurements, satisfaction (10-point scale) and measurement time (min) were assessed. Validity outcomes included perceived exertion, and optimal stiffness based on minimizing walking EC.

Results

The ADJUST-AFO measurement time took 168±33 min, compared to 211±26 min for the manual procedure, $p = 0.041$. Satisfaction were identical between procedures (ADJUST-AFO = 7.61±0.39, manual = 7.61±0.49), $p = 0.994$. Exertion was higher for the ADJUST-AFO procedure (5.46±2.50) compared to the manual procedure (4.6±2.2). The optimal stiffness was the same for both procedures in 4/6 patients, while in the other two patients the optimal stiffness differed maximum 1.0 Nm/deg.

Conclusion

Our preliminary results demonstrate that the ADJUST-AFO is a feasible and potentially valid tool for selecting the optimal AFO stiffness in people with calf muscle weakness. It reduced optimization time by 30% compared to the manual procedure, without adverse events. The optimal stiffness value was within 1 Nm/degree difference between the ADJUST-AFO and the manual procedure. Further validation of the ADJUST-AFO requires an analysis of the gait biomechanical and the inclusion of additional patients for a more precise estimate of the validity.

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PERSONALIZED REHABILITATION IN SEVERELY FATIGUED MYOSITIS PATIENTS (PRO-FIT): STUDY PROTOCOL OF A PILOT RANDOMIZED CONTROLLED TRIAL

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Introduction Myositis is the most prevalent acquired muscle disorder in adults. Despite an initial favorable effect of immunosuppressive treatment most people suffer from long-standing disability. Severe fatigue is highly prevalent (70-90%), leading to decreased daily functioning, participation, and quality of life. Disease-related healthcare costs, including societal costs, are 3 to 5 times higher than those of the general population. This highlights the need for interventions aimed at improving functional outcomes and return-to-work. Personalized rehabilitation therapy, including remotely delivered cognitive behavioral therapy (CBT), exercise therapy (ET), or both, is likely (cost)effective compared to usual care in the chronic phase of myositis. A pilot study is first needed to estimate the effect size of the intervention.

Purpose To answer the following questions: (1) What is the estimated effect size of personalized rehabilitation therapy for improving daily functioning in severely fatigued myositis patients, compared to usual care? (2) What are the societal costs of personalized rehabilitation therapy compared to usual care amongst severely fatigued myositis patients?

Method This multicenter trial randomly assigns participants to the intervention (6 months of personalized rehabilitation therapy) or the control group (usual care). Twenty patients aged 18–68, diagnosed with stable myositis (excluding inclusion body myositis) for at least 12 months and experiencing severe fatigue, will participate. The appropriate treatment (ET, CBT, or both) is determined in consultation with a rehabilitation physician. Outcomes will be assessed through an exercise test, questionnaires, interviews, and activity monitoring. The primary endpoint is the change in daily functioning, measured by the Canadian Occupational Performance Measure (COPM).

Results Five participants have been randomized, and baseline data (n = 5) have been collected, showing a mean COPM performance score of 5.6 (SD = 0.6). The mean CIS-Fatigue score was 40.4 (SD = 3.6), and physical fitness, measured as VO_2peak, averaged 27.7 ml/min/kg (SD = 11.0).

Conclusion The study protocol is ongoing, with participants receiving the intervention. Inclusion of further participants and continued data collection are necessary to estimate the effect size of personalized rehabilitation therapy.

CONSENSUS-BASED STANDARDIZED MEASURES FOR A NATIONAL GNAO1 REGISTRY: A MODIFIED DELPHI PROCEDURE

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Introduction: GNAO1-associated disorder (GNAO1-AD) is a rare genetic neurological disorder with various clinical manifestations including movement disorders (MDs), epilepsy and developmental delay, and a broad spectrum of severity. New interventions have recently become available to manage MDs and advancements are made in current interventions, such as deep brain stimulation. The heterogeneous presentation poses a challenge to identify standardized measures to monitor functioning, disease progression and response to interventions.

Purpose: To determine standardized measures for a Dutch GNAO1 registry, using consensus-based recommendations from a panel of experts, consisting of healthcare professionals and people with lived experience. Primary outcome was consensus-based agreement, divided into three levels of recommendation using agreement rates (A=100%; B=75-99%; C=50-74% OR >75% and with >25% neutral votes).

Methods: Standardized measures were identified through a systematic literature search and a survey amongst stakeholders. Data was used to construct the Delphi query into a web-based software (www.edelphi.org). The International Classification of Functioning, Disability and Health model (ICF-model) was used to structure statements accordingly, in order to cover all health-related domains. International experts on GNAO1-AD including patient representatives were invited to join the panel, and to participate in the procedure for six weeks. Panel members could visit the platform to vote, comment and discuss at any time, there were no voting rounds. Ratings were based on a 5-point Likert scale.

Results: Eight domains within the ICF-model were identified in the survey, and 32 standardized assessment instruments were identified in both survey and systematic search, ultimately, resulting in 67 statements incorporated in the Delphi query. The panel (27 healthcare professionals; 10 parents) recommended 17 domains (level A=4; level B=13; Fig. 1) and 29 standardized assessment instruments (level B=8; level C=21).

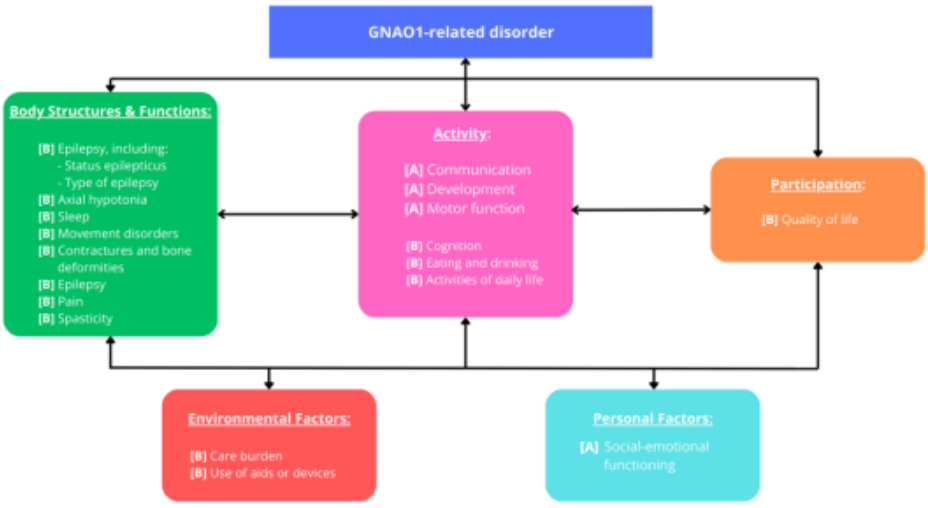

Figure 1. *Consensus-based inclusions per domain in the ICF-model*

Conclusions: In this study, consensus on standardized measures for in a Dutch GNAO1 registry was achieved, based on expertise from professionals and people with lived experience. These results may lead to a more uniform approach for future registries and clinical trials on new interventions for MDs.

Safety and accuracy assessment of pedicle screw insertion using 3D-printed guides based on MRI-based, AI-generated synthetic CT: a cadaver study

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Hypothesis: We hypothesize that sCT-based guides perform comparably to CT-based guides in terms of linear and angular deviations from the preoperative planning and pedicle breach rate.

Introduction: The use of 3D-printed patient-specific guides has shown to provide highly accurate pedicle screw placement in the treatment of paediatric spinal deformities. Although computed tomography (CT) volumes are derived using low-dose imaging protocols, they still expose the young patient to considerable levels of ionizing radiation. AI-generated MRI-based synthetic CT (sCT) provides in vivo morphology of the posterior elements, radiation free. The aim of current study was to assess the accuracy of pedicle screw instrumentation achieved by the use of sCT based 3D-printed patient-specific guides.

Methods: CT and sCT volumes of four human cadaveric spines were obtained, followed by the digital planning of pedicle screws in a selective subset of vertebrae. A total of 62 2.0 mm K-wires were inserted through the 3D-guides to simulate pedicle screw insertion, of which 30 using sCT based 3D-guides and 32 using CT based 3D-guides. K-wire insertion accuracy was evaluated by superimpose analysis of preoperative- and postoperative trajectories, as well as the postoperative grading of the cortical breach rate using the Gertzbein-Robbins scale.

Results: Median linear entry-point deviations were 0.99 mm vertically and 0.52 mm horizontally for sCT, compared to 0.99 mm and 0.46 mm for CT. Angular deviations in the transverse plane were 1.02° for sCT and 0.94°for CT, with sagittal angular deviations of 1.84°and 2.05°respectively. No significant differences between sCT-based or CT-based 3D guides were observed in any parameter ($p>0.05$). The postoperative grading of pedicle's cortical breach showed 100% of the K-wires placed in the 'safe zone' for both sCT and CT.

Conclusion: Superimpose analysis showed non-inferior results in terms of postoperative linear- and angular deviations from the preoperative planning for sCT based 3D-guides compared to CT based 3D-guides. Additionally, analysis of pedicle's cortical breach rate showed no difference between both modalities, both 100% safe with minimal or no pedicle breach. These findings represent a relevant step towards the clinical application of sCT in the radiation-free insertion of pedicle screws using 3D-printed patient-specific guides.

THE EFFECT OF LOW-DOSE CYCLIC 17-β-ESTRADIOL ADMINISTRATION ON BONE TURNOVER IN HEALTHY POSTMENOPAUSAL WOMEN: A RANDOMIZED CONTROLLED TRIAL

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Introduction: Hormone therapy containing estrogen is an effective treatment for the prevention of bone loss in low-estrogenic states. Apart from the inhibiting effect on bone resorption, studies have demonstrated that 17-β-estradiol also increases bone formation in the first 4 weeks of treatment.

Purpose: We hypothesized that this initial increase in bone formation is driven by a rise in serum 17-β-estradiol, as seen during the menstrual cycle of premenopausal women. Therefore, we investigated whether restoring a monthly cycle in 17-β-estradiol levels is beneficial for bone formation.

Methods: Healthy postmenopausal women, aged 45-60 years, were randomized to open-label transdermal cyclic (4-week cycle: 2 weeks 25 mcg/24h, and 2 weeks 50 mcg/24h), continuous low-dose (25 mcg/24h), or continuous standard-dose 17-β-estradiol (50 mcg/24h) for 16 weeks. All participants also received oral micronized progesterone 100 mg once daily. Endpoints of the study were the interaction between treatment and time on serum P1NP (bone formation) and on serum CTX (bone resorption). We measured P1NP and CTX every two weeks.

Results: The 48 participants had a mean age of 53.5 (SD 3.3) and had their final menstrual period at 50.5 (SD 3.8) years. P1NP increased in all groups between baseline and week 4, followed by a decrease between week 4 and week 16. The median decrease in P1NP was lower in the cyclic (-12.6 µg/L (IQR -20.4 – -0.7), $p = 0.03$) and low-dose group (-12.0 µg/L (IQR -18.4 – 1.8), $p < 0.01$) compared to the standard-dose group (-15.2 µg/L (IQR -29.1 – -8.7)). CTX decreased between baseline and week 16 in all groups. The median decrease in CTX from baseline until week 16 was similar in the cyclic group (-143 ng/L (IQR -221.3 – -71.2), $p = 0.45$) compared to the standard-dose group (-176.9 ng/L (IQR -218.9 – -123.2)). However, CTX values remained higher in the low-dose group (-112.2 ng/L (IQR -192.6 – -67.9), $p = 0.04$) compared to the standard-dose group.

Conclusion: Cyclic 17-β-estradiol administration resulted in higher bone formation over time compared to continuous standard-dose administration, while bone resorption did not differ between the cyclic and continuous standard-dose group. Thus, cyclic estradiol may improve bone health in the short-term.

THE EFFICACY OF A BLENDED INTERVENTION TO IMPROVE PHSYICAL ACTIVITY AND PROTEIN INTAKE FOR OPTIMAL PHYSICAL RECOVERY AFTER ONCOLOGICAL SURGERY : A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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Introduction: There is a need for supportive care interventions to improve physical activity and nutritional status in patients after oncological surgery. Interventions using smartphone apps and activity trackers could offer a promising solution as they integrate behavioural change techniques, such as self-monitoring, which can increase patient engagement and support improvements in physical activity and protein intake. Therefore, we developed the Optimal Physical Recovery After Hospitalization (OPRAH) intervention.

Purpose: To evaluate the efficacy of the OPRAH intervention to improve physical activity and protein intake after hospital discharge on recovery of physical functioning in patients after gastrointestinal or lung cancer surgery.

Method: A multicenter single-blinded RCT was performed in adults undergoing curative gastrointestinal or lung cancer surgery. Patients were randomized to the control group (usual care) or intervention group, who received a smartphone app, accelerometer, and remote coaching from a physiotherapist and dietician in addition to usual care for three months after hospital discharge. Study outcomes were measured prior to surgery and one, four and eight weeks and three and six months after hospital discharge. The primary outcome was recovery in physical functioning up to six months after surgery measured with the CAT PROMIS Physical Functioning (PROMIS PF). The most important secondary outcomes were physical activity and protein intake.

Results: A total of 163 patients were analysed (90 control, 73 intervention). The mean PROMIS PF of the intervention group was 36.0 at one week, 46.6 at three months and 47.8 at six months. The mean PROMIS PF of the control group was 35.1 at one week, 43.8 at three months and 45.7 at six months. The overall intervention effect on physical functioning was not significant in the intention-to-treat analyses (B 1.4, $p = 0.08$), yet was significant in the per-protocol analyses (B 2.1, $p = 0.01$). The intervention significantly improved physical activity (B 9.7, $p < 0.01$) and protein intake (B 9.8, $p < 0.01$).

Conclusion: The OPRAH intervention contributes to an improvement in physical activity and protein intake after oncological surgery. If there is sufficient adherence to the intervention, the OPRAH intervention contributes to better and faster recovery in physical functioning.

ENHANCING RETURN TO DAILY LIFE ACTIVITIES, INCLUDING WORK AND SPORT, AFTER KNEE ARTHROPLASTY WITH A PERSONALIZED EHEALTH CARE PROGRAM – RESULTS OF THE MULTICENTRE ACTIVE RANDOMIZED CONTROLLED TRIAL

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Introduction
After knee arthroplasty, there is little guidance on return to daily life activities, including work and sport, despite the importance of these outcomes, especially for patients in working-age. Personal eHealth programs could provide perioperative guidance to patients, facilitating earlier recovery.

Purpose
This study evaluated whether an additional personalized eHealth care program enhances return to daily life activities, including work and sports, compared to usual care among working-age knee arthroplasty patients in the Netherlands.

Method
The multicenter randomized controlled ACTIVE trial was conducted across eleven Dutch medical centers. Eligible patients were working-age patients on the waiting list for a primary total- or unicompartmental knee arthroplasty, employed at least eight hours a week, and willing to return to work. Patients were randomized 1:1 into the intervention or control group. The intervention group received an eHealth care program in addition to usual care, including an eHealth application with activity tracker, goal attainment scaling and a one-time case-manager consultation. The control group received usual care. The primary outcome was determined with the self-reported PROMIS-Physical Functioning, assessing time from surgery to return to eight self-selected daily life activities including work and sport. Kaplan-Meier curves and a multi-level longitudinal Cox proportional hazards models were used for analysis. Thereby, several potential covariates were taken into account like body mass index, knee demanding work, and the variables used for stratification (total or unicompartmental knee arthroplasty, participating centres with or without eHealth as usual care, and recovery expectations).

Results
From October 2020 through January 2023, 293 patients were included, with 145 in the intervention group (52% female, mean age 58 years) and 142 in the control group (51% female, mean age 59 years). Median time to resume the self-selected daily life activities was 49 days (IQR 31 – 81) in the intervention group and 72 days (IQR 36 - 142) in the control group, representing a 23-day difference (HR 1.7,95%CI 1.4 – 2.2).

Conclusion
The personalized eHealth care program reduced the time to return to the self-selected daily life activities including work and sport by 23 days compared to usual care.

BODY COMPOSITION AND OVERWEIGHT IN INDIVIDUALS WITH NEUROMUSCULAR DISEASES

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Introduction In individuals with slowly progressive neuromuscular diseases (NMD), muscle mass decreases over time due to the combined effects of disease pathology, inactivity, and aging. This leads to muscle weakness, fatigue, and pain, making physical activity challenging and reducing energy expenditure. The low energy expenditure consequently poses a risk for developing overweight and related health issues. Understanding body composition differences between overweight and healthy weight individuals with NMD is essential before implementing weight loss interventions.

Purpose To investigate the body composition, including fat mass (FM) and fat-free mass (FFM), of overweight and healthy weight individuals with NMD.

Methods Body composition and anthropometric data (weight, height and body mass index (BMI)) were cross-sectionally measured in participants with different NMD. Air displacement plethysmography (BODPOD) was used to measure body composition. FM (kg, %), FFM (kg, %), FM index (FMI (kg/m^2)) and FFM index (FFMI (kg/m^2)) were compared between overweight (BMI ≥25 kg/m^2) and healthy weight (BMI 18.5-25 kg/m^2) participants. FFMI (kg/m^2) was compared to reference values[1].

Results Twenty-eight participants diagnosed with post-polio syndrome, Charcot-Marie-Tooth disease and inclusion body myositis were included (aged 33-79 years, 46% female). Twelve participants (43%) had overweight. Overweight participants had a higher FM (kg), FMI and FFMI compared to participants with a healthy weight (33.2±10.8 kg vs 25.1±5.2 kg, 11.8±4.4 kg/m^2 vs 8.0±1.6 kg/m^2, 17.4±1.8 kg/m^2 vs 15.2±1.5 kg/m^2 (all $p<0.01$)). FFM (kg), FM (%) and FFM (%) did not differ ($p>0.05$). 81% of the healthy weight participants and 8% of the overweight participants had a very low FFMI (<10^{th} percentile).

Conclusion The results of this study suggest that when accounting for height, both FM and FFM are higher in overweight compared to healthy weight individuals with NMD. Moreover, it suggest that a significant proportion of healthy weight participants exhibit a critically low FFMI. This underscores the importance of investigating strategies to alter body composition rather than body weight in individuals with NMD.

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STATIC AND DYNAMIC EVALUATION OF FOOT POSTURE IN ANKLE-FOOT ORTHOSES IN CHILDREN WITH CEREBRAL PALSY: STUDY PROTOCOL

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Introduction: More than 90% of children with cerebral palsy (CP) develop foot deformities [1], leading to pain and gait problems. It has been shown that the altered external loading due to abnormal movements and posture may contribute to progression of the deformity, highlighting the importance of early interventions to realign the foot [2]. In addition, if the foot is adequately corrected, the function of the foot as a lever arm during walking can be improved [3]. To improve gait and correct deformities, the majority of children with CP wear ankle-foot orthoses (AFOs) during growth. However, as the AFO covers the foot and lower leg, assessing foot posture within the AFO is challenging, especially during walking. Therefore, the true extent of foot posture correction by the AFO is not yet known.

Purpose: To evaluate the effect of AFOs on foot posture and function in children with CP during standing and walking.

Method: 25 children with CP (4-18 years old) wearing an AFO will be included, as well as 20 typically developing (TD) children. Static foot posture (relative position and orientation of the bones) within the AFO and barefoot will be assessed using weight-bearing cone-beam computed tomography (WBCT) scans. Dynamic foot posture during walking will be assessed through plantar pressure measurements, in three conditions: (1) barefoot with a pressure plate; (2) with non-correcting confection shoes using pressure soles; and (3) with their own AFOs and shoes, also using pressure soles. All outcomes will be compared between conditions with and without the AFO, and with TD children.

Results: We expect improvement in both static and dynamic foot posture when wearing the AFO. Furthermore, we expect the improvement in foot posture correction to be participant- and AFO-specific.

Conclusion: With this study, we will gain novel insight into the extent of foot posture correction of children with CP while wearing an AFO, and possible directions for improvement of AFOs. This will lead to important insights into the working mechanism of AFOs, and more targeted application of treatment for children with CP who are at a high risk of developing a foot deformity.

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EXPLORING BIOMECHANICAL AND USER-RELATED OUTCOMES IN FOOTWEAR DESIGN FOR INDIVIDUALS WITH DIABETES AT MODERATE-TO-HIGH RISK OF ULCERATION: A KNOWLEDGE GAP ANALYSIS

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Introduction Diabetes impacts 537 million individuals globally. Approximately 19 to 34% of those develop a foot ulcer during their lifetime, with a high risk of recurrence and subsequent lower limb amputations. International guidelines recommend providing custom-made footwear to individuals with diabetes at high risk of foot ulceration. For these individuals, current footwear design principles often seem to rely on studies in the non-targeted population, misrepresenting actual biomechanical and user-related needs.

Purpose We aimed to identify and summarise knowledge gaps in biomechanical and user-related outcomes in footwear designs for individuals at moderate-to-high risk of foot ulceration.

Method We did a systematic literature search in PubMed and EMBASE using terms related to footwear interventions and biomechanical and user-related outcomes, including only experimental studies in English. Two reviewers screened titles, abstracts, and full texts for eligibility. Included publications were categorised into subject groups: population, 5 interventions and 7 outcomes (4 biomechanical and 3 user-related outcomes). A table presented the number of papers available for each footwear component and outcome, indicating the number of evidence available per category. The publication count per combination identified the extent of the knowledge gaps.

Results Of the 5813 papers identified, 289 were included, with 92% inter-observer eligibility agreement. Of these, 13% provided direct and 87% indirect evidence. Biomechanical and user-related outcomes were studied in 60% and 40% of the publications in direct evidence. For 60% of the interventions, none or <5 studies were done in the target population. While pressure distribution was commonly studied (n=11) about the insole, pressure measurements were not studied in the upper and midsole of the footwear. Shear, the centre of pressure, and quality of life lacked direct evidence.

Conclusion This analysis identified three major gaps in the literature about the effects of footwear on biomechanical and user-related outcomes in individuals with diabetes at moderate-to-high risk of foot ulceration. There was limited to no evidence on the population of interest, user-related outcomes, and upper footwear components. Addressing these gaps is essential to obtain more valid outcomes on footwear design efficacy. We emphasise the need to prioritise research on user needs and upper footwear components.

A WORLDWIDE SURVEY FROM INDICATION TO REHABILITATION IN SELECTIVE DORSAL RHIZOTOMY

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Abstract

Introduction Selective dorsal rhizotomy (SDR) is a neurosurgical treatment used worldwide to reduce spasticity. The procedure has undergone many changes since its introduction in the early 1900s, and currently, different centers vary in many aspects of the procedure.

Purpose We surveyed centers on different continents regarding SDR indications, surgical techniques, and postoperative rehabilitation to provide greater insight.

Methods Ten centers, based on five continents, with SDR experience participated in an online survey preparing for a pre-conference workshop in 2022. The main topics were patient characteristics, the selection process, surgery, and rehabilitation.

Results Universal suitable candidates for SDR were patients with bilateral spastic cerebral palsy, Gross Motor Function Classification System levels II or III, ages five to seven years, and adequate strength, motor control, and access to postoperative rehabilitation. Centers differed in additional inclusion and exclusion criteria and the use of diagnostic tools. Both single- and multilevel approaches were used, with electrophysiological monitoring applied in all approaches. Intensive rehabilitation was recommended after surgery, followed by a less intensive program, with variations in duration, therapy frequency, modalities used, and follow-up periods.

Conclusion This survey demonstrated many similarities in several aspects of the SDR procedure in centers performing SDR worldwide, while considerable variability was also seen. The results emphasize the need for standardized reporting of SDR procedures and outcome measures to enable international comparative studies. A Delphi procedure could be a first step to reaching a consensus on outcome measurements, which may lead to a consensus regarding the most suitable candidates, surgical techniques, and rehabilitation programs to improve functional outcomes.

THE IMPACT OF MULTIDISCIPLINARY TRANSITIONAL CARE INTERVENTIONS FOR COMPLEX CARE NEEDS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction The number of older patients and/or patients with multimorbidity has increased in the last decades, leading to an increased complexity of care delivery. Multidisciplinary transitional care interventions (MTCIs) ensure care coordination and continuity after hospital discharge while addressing (older) patients' rehabilitation needs—including physiotherapy, occupational therapy, speech and language therapy, and/or nutrition.
Purpose To identify, critically appraise, and synthesize randomized controlled trials investigating the impact of MTCIs on hospital readmissions, mortality, patient satisfaction, quality of life, and physical, cognitive, and psychological status.
Methods Medline, Embase, CINAHL, and CENTRAL were searched for randomized controlled trials assessing MTCIs' impact on readmissions, mortality, and health-related outcomes (inception–July 2024). Risk of bias was evaluated with the Risk of Bias-2 tool. Subgroup analyses assessed whether different intervention types affected outcomes differently. Certainty of evidence was assessed with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, considering overall risk of bias, consistency, precision, directness, and publication bias rather than mere statistical significance. Subgroup analyses were interpreted with the Instrument to evaluate the Credibility of Effect Modification Analyses (ICEMAN).
Results Forty-nine trials (25,566) patients were included. MTCIs likely reduced readmissions (RR=0.88; 95%CI:0.80 to 0.96, low certainty) and mortality (RR=0.92; 95%CI:0.84 to 1.01, high certainty). They showed low to moderate certainty in improving physical (SMD=0.54; 95%CI: -0.06 to 1.15) and mental (SMD=0.44; 95%CI: -0.08 to 0.96) quality of life, patient satisfaction (SMD=0.49; 95%CI: -0.14 to 1.12), and physical performance (SMD=0.49; 95%CI: -0.11 to 1,10). Subgroup analysis revealed a larger effect on physical performance in more complex interventions (SMD=0.83; 95%CI:0.02 to 1,65). Results were inconclusive for psychological distress and cognition. Heterogeneity was high across studies (I^2>75%).
Conclusion This review comprehensively examines MTCIs, suggesting they may reduce readmissions and mortality while improving quality of life and physical performance. Using rigorous methodology (GRADE, ICEMAN), it provides a solid foundation for clinical decision-making. However, given varying effects across comparisons, tailored implementation strategies are needed to maximize MTCIS' beneficial effects on readmissions and health-related outcomes. A systematic needs assessment before intervention implementation may enhance success. Further research should explore how to optimize intervention strategies for different settings and populations.

USING THE HOOS AND KOOS IN POST-ARTHROPLASTY PHYSIOTHERAPY: A SURVEY

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Introduction: Physiotherapy guidelines recommend using the Hip and Knee Osteoarthritis Outcome Score (HOOS/KOOS) and their physical functioning short forms (HOOS-PS/KOOS-PS) following total hip and knee arthroplasty (THA/TKA). However, it remains unclear to what extent and for what reasons these questionnaires are applied by physiotherapists in daily clinical practice.
Purpose: To explore the frequency of administration and reasons for using the HOOS(-PS) and KOOS(-PS), as well as their determinants, among physiotherapists after THA and TKA.
Method: An online survey targeting primary care physiotherapists with experience treating at least five patients with a THA or TKA in the past five years was distributed via email and peer-to-peer recruitment. The survey included sociodemographic characteristics, seven questions on HOOS(-PS)/KOOS(-PS) use, and 27 statements assessing physiotherapists' attitudes, knowledge, and organizational context regarding patient-reported outcome measures (PROMs) in general. Based on their reasons for using HOOS/KOOS, respondents were categorized as "passive users" (those who administered them due to organizational requirements or guideline recommendations), "active users" (those who used them for individual patient treatment purposes), or "non-users" (those who did not administer the HOOS(-PS) or KOOS(-PS)). Descriptive statistics were used to explore determinants associated with active use.
Results: A total of 166 physiotherapists completed the survey (median age: 40.0 years, female: 34%, median experience: 15.0 years). The minority (19%) were non-users. Among the remaining 81%, 25% were passive users, while 56% were active users.
Among the active users, 84% primarily used HOOS(-PS)/KOOS(-PS) for treatment evaluation, whereas 39% or less used them for diagnosis, prognosis, patient education, shared decision-making, and/or clinical decision-making. Most active users (68%) reported "often" or "always" discussing HOOS/KOOS outcomes with patients.
Determinants associated with active use of the HOOS(-PS)/KOOS(-PS) included fewer years of experience as a physiotherapist, a larger treatment volume of THA/TKA, a younger age, and a more positive attitude toward using PROMs.
Conclusion: Most physiotherapists administer the HOOS(-PS)/KOOS(-PS), but their use in daily clinical practice is limited. Active users tend to be younger, less experienced, treat a larger volume of THA/TKA patients, and have a more positive attitude toward using PROMs.

(COST-)EFFECTIVENESS OF PERSONALISED MULTIMODAL PHYSIOTHERAPY COMPARED TO SURGERY IN PATIENTS WITH PAINFUL CERVICAL RADICULOPATHY. PROTOCOL OF A RANDOMIZED NON-INFERIORITY TRIAL (THE MOVE-IT STUDY)

Authors

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ABSTRACT

Introduction: Painful cervical radiculopathy (CR) is a disorder that can lead to severe limitations in activities and participation. Surgery is considered when conservative treatment does not lead to relevant improvements or when neurological signs are severe. However, personalized multimodal physiotherapy may offer non-inferior outcomes to surgery for painful CR, with possibly fewer adverse events and lower costs. Therefore, research is needed about the (cost-)effectiveness of personalized multimodal physiotherapy compared to surgery.

Purpose: to investigate whether personalized multimodal physiotherapy compared to ACDF surgery is non-inferior over a 12 month period and (cost-)effective in patients with painful CR who have an indication for surgery.

Methods: We conduct a randomized non-inferiority trial to compare personalized multimodal physiotherapy surgery (1:1 allocation ratio) among 126 patients with painful CR. Patients are recruited by neurologists in 10 Dutch hospitals. The personalized multimodal physiotherapy consists of a mechanism-based approach using a biopsychosocial framework and is tailored to the individual patient. Anterior cervical discectomy with fusion is the comparison treatment. Primary outcome is neck pain disability over 12 months, measured using the Neck Disability Index with a prespecified non-inferiority margin of three points. Secondary outcomes are arm and neck pain intensity, global perceived effect, quality of life, patient-specific activities, activity limitations, patient acceptable symptom state, fear of movement, knowledge about pain, and complications. All outcomes are measured at baseline and at three, six, nine, 12 months follow-up. Moreover, to assess how the treatment effect proceeds in time additional measurements will be performed at 24 and 60 months follow-up. A parallel process evaluation and cost-effectiveness analysis will be performed. Data analysis will be performed according to 'intention-to-treat' and 'as-treated' principles using linear and logistic mixed model analyses.

Results and conclusion: Recruitment commenced in May 2024. All data are anticipated to be collected by December 2026 when data analysis and interpretation will commence. Results and conclusion will be available after this.

USER EXPERIENCES AND PRELIMINARY EFFECTS OF THE CUE2WALK SMART CUEING DEVICE FOR FREEZING OF GAIT IN PEOPLE WITH PARKINSON'S DISEASE

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Introduction One of the most disabling motor symptoms of Parkinson's Disease (PD) is Freezing of Gait (FoG), which is characterized by the sudden, transient, and involuntary inability to produce ongoing forward locomotion. FoG impairs mobility and increases the risk of falls, leading to reduced quality of life in people with PD. While drug treatments offer limited relief, non-pharmacological interventions such as external cueing have shown promise in managing FoG. The Cue2walk, a wearable smart cueing device, was developed to detect FoG episodes and hereupon provide rhythmic external cues in the form of sound and/or vibration to help people with PD manage FoG in daily life.

Figure 1. The Cue2walk device

Purpose To determine the user experiences and preliminary effects of using the Cue2walk on FoG symptoms and health-related quality of life (QoL).

Methods In this open-label pilot study, 17 current users of the Cue2walk participated. Data were collected through an online questionnaire, which included the EQ-5D-5L scale for health-related QoL, additional Parkinson's-specific questions, and a Net Promoter Score (NPS) for customer satisfaction.

Results 81% of the respondents reported to experience positive effects on FoG duration, 75% on falls, 63% on daily activities and 62% on self-confidence. Health-related QoL increased from 5.2/10 to 6.1/10 and responders' average NPS was 7.8/10. No negative effects were reported. A moderately strong correlation ($r=0.64$, $p<0.05$) was observed between longer device usage per day and greater positive impact on daily activities.

Conclusion This study suggests that the Cue2walk is a valuable tool for managing FoG and enhancing QoL in people with PD. Further research with larger populations and extended follow-up is recommended to validate these findings and to assess the long-term efficacy and cost-effectiveness of the device.

APPLYING MOVEMENT BEHAVIOR INTO DAILY LIFE: EXPERIENCES OF PATIENTS WITH CHRONIC MUSCULOSKELETAL PAIN AND PHYSICAL THERAPISTS – A QUALITATIVE STUDY

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Introduction

Patients with chronic musculoskeletal pain (CMP) face challenges in their daily activities. Physical therapists can help address these issues using strategies that focus on patients' movement behavior. However, applying new movement behavior into patient's own context remains a challenge.

Purpose

The aim of this study is to explore the experiences of patients with CMP and physical therapists in applying improved movement behavior in a patient's daily life.

Method

We conducted semi-structured face-to-face interviews with patients with CMP who had completed exercise therapy. Additionally, we organized focus groups with physical therapists experienced in guiding CMP patients. Participants were selected using a purposive sampling strategy. Both the interviews and focus groups used interview guides that included semi-structured open-ended questions. All interviews and focus groups were audio-recorded, transcribed verbatim, and independently analyzed by two researchers using thematic analysis.

Results

A total of sixteen interviews with patients and two focus groups were analyzed. Four main themes emerged from the patient data: (1) learning by doing, (2) awareness and insights, (3) continuous focus on context, and (4) conditional factors, such as having a strong connection with the practitioner. From the therapist data, three main themes revealed: (1) continuous focus on patient's context, (2) strong patient-therapist connection as a conditional factor, and (3) exercise-specific guidance, such as experienced-based learning and promotion of self-efficacy.

Conclusion

Both patients and therapists experienced the continuous focus on the context for optimizing the application of movement behavior in patients' daily lives. Both groups also perceived the importance of good therapist-patient connection. Experience-based learning is another valuable component for applying movement behavior in the patient's own daily life.

MONITORING CANCER-RELATED FATIGUE USING A SMARTPHONE APPLICATION: A MIXED-METHODS STUDY PROTOCOL

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Introduction
Cancer-related fatigue (CRF) is a prevalent and debilitating symptom affecting over 50% of cancer survivors, significantly impairing quality of life and daily functioning. Unlike typical fatigue, CRF persists despite adequate rest and is influenced by multiple factors such as occupation, stress, and sleep quality. Digital biomarkers, collected through technologies like smartwatches and smartphones, offer a promising approach for CRF monitoring. These technologies provide objective data on activity levels, heart rate variability, and sleep patterns, while ecological momentary assessment (EMA) methods enable contextual monitoring.

Integrating smartwatch data with smartphone applications may enhance self-management of CRF, empowering patients to monitor fatigue-related factors and receive personalized feedback. Such applications could also support healthcare professionals by facilitating remote monitoring and tailored interventions. Despite the potential benefits, little is known about how patients and healthcare professionals experience this new approach of using a smartphone application within therapy.

Purpose
This study will investigate the usability and perceived impact of a smartphone application combining wearable and self-reported data for CRF management among patients with CRF and healthcare professionals treating them.

Methods
A mixed-methods study will be conducted between May and September 2025. Participants include 10 primary care healthcare professionals and two to four of their patients with CRF. The six-week intervention, adding to conventional therapy, involves using the *Healthy Chronos* smartphone application, which integrates short EMA questionnaires on energy levels, mood, and sleep quality with smartwatch-derived activity data. Healthcare professionals will access patient data via a therapeutic dashboard.

Data collection includes pre- and post-intervention surveys including demographic questions and assessing patients' CRF severity. The post-intervention survey also assesses usability (System Usability Scale), motivation (Intrinsic Motivation Inventory), and overall satisfaction (Net Promoter Score). Adherence data will be tracked through app usage metrics. Semi-structured interviews will be performed after the intervention and will explore user experiences, perceived effectiveness, and impact on patient-healthcare professional interactions.

Quantitative data will be analysed using descriptive statistics and qualitative data will be analysed using thematic analysis.

Discussion
This study aims to provide insights into the feasibility and acceptability of a digital health intervention for CRF, informing future developments in eHealth-supported cancer rehabilitation.

Assessing the relationship between protein intake, physical activity, and muscle mass in ambulant children with cerebral palsy: early findings from the Power2Walk study.

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Introduction: Muscles of children with cerebral palsy (CP) deviate structurally and are often reduced in mass when compared to typically development (TD), which is likely due to differences in muscle development. Interestingly, it remains unknown whether muscles of children with CP respond similarly to anabolic stimuli like physical activity and protein intake when compared to muscles of TD children. Therefore, we explored whether lean mass is related to protein intake and physical activity levels in children with CP.

Methods: Up to now, nine children with CP (ages 5-12; GMFCS I-III) were included. Lean mass was measured using bioelectrical impedance analysis (BodyStat Quadscan 4000). Daily protein intake was recorded via 3-day parent-reported food diaries and physical activity was tracked using wrist-worn accelerometers (ActiGraph wGT3X). We assessed relationships between lean mass, protein intake, and physical activity using age-adjusted parametric multiple linear regression ($\alpha \leq 0.05$).

Results: All subjects (average 2.57 ± 1.13 g kg^{-1} day^{-1}) met their age specific daily recommended protein intake. The regression model showed a positive association ($F = 17.09$; $p = 0.003$; $R^2 = 0.85$) with a significant effect for age ($p = 0.001$) but not protein intake ($p = 0.292$). Physical activity data was still unavailable for analysis and will be presented at AMS-day 2025.

Conclusion: We conclude that protein intake is not significantly associated with lean mass in this subset of children. We plan to further investigate whether protein intake relates to increases in lean mass in children with CP following a functional power training program.

The effectiveness of the Back At work After Surgery (BAAS) care pathway on return to work for patients receiving knee arthroplasty: a one year multicenter matched controlled trial in the Netherlands

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Abstract:
Background: Considering the increase in the demand from working age patients seeking KA and the low RTW rates after KA care, optimization of care for patients getting KA with a focus on RTW is essential. We evaluated a work-integrated care pathway—Back At work After Surgery (BAAS)—aimed at improving RTW outcomes compared with usual care in the Netherlands.
Method: In this multicenter matched controlled cohort study, working patients who had primary KA were included. Patients in two Dutch hospitals (BAAS cohort, n=145) received integrated medical and occupational care, including structured pre- and postoperative consultations, goal setting, activity tracking and interdisciplinary team meetings with both medical and occupational health professionals (fig 1). Two separate control cohorts (Expect TO work: n=179; ACTIVE: n=133) from 15 hospitals/clinics received usual care. The primary outcomes were the time to first day of RTW and time to full RTW within 12 months, both self-reported.
Findings: A total of 457 patients were included (BAAS n=145; Expect TO work n=179; ACTIVE n=133). The median time to first day of RTW was 16-25 days shorter in the BAAS cohort (27 days) compared to Expect TO work (52 days; hazard ratio [HR] 2.7; 95% confidence interval [CI]:2.1-3.4) and ACTIVE (43 days; HR:1.95; CI:1.5-2.6). At three months, 90% of BAAS patients had started RTW versus 63% and 76% in the control cohorts. BAAS patients also achieved full RTW earlier, with a median time reduced by 27 days compared to ACTIVE (HR:1.4; CI:1.1-1.8; p=0.01). The odds of full RTW at 12 months were significantly higher in the BAAS cohort compared to Expect TO work, namely odds ratio (OR) 3.9 (CI:1.2-12.9) and ACTIVE OR 9.3 (CI:2.9-29.7).
Conclusions: The BAAS work-integrated care pathway was more effective than usual care in improving RTW outcomes after knee arthroplasty in the Netherlands.
Funding: ZonMw (reference 10320052010006).

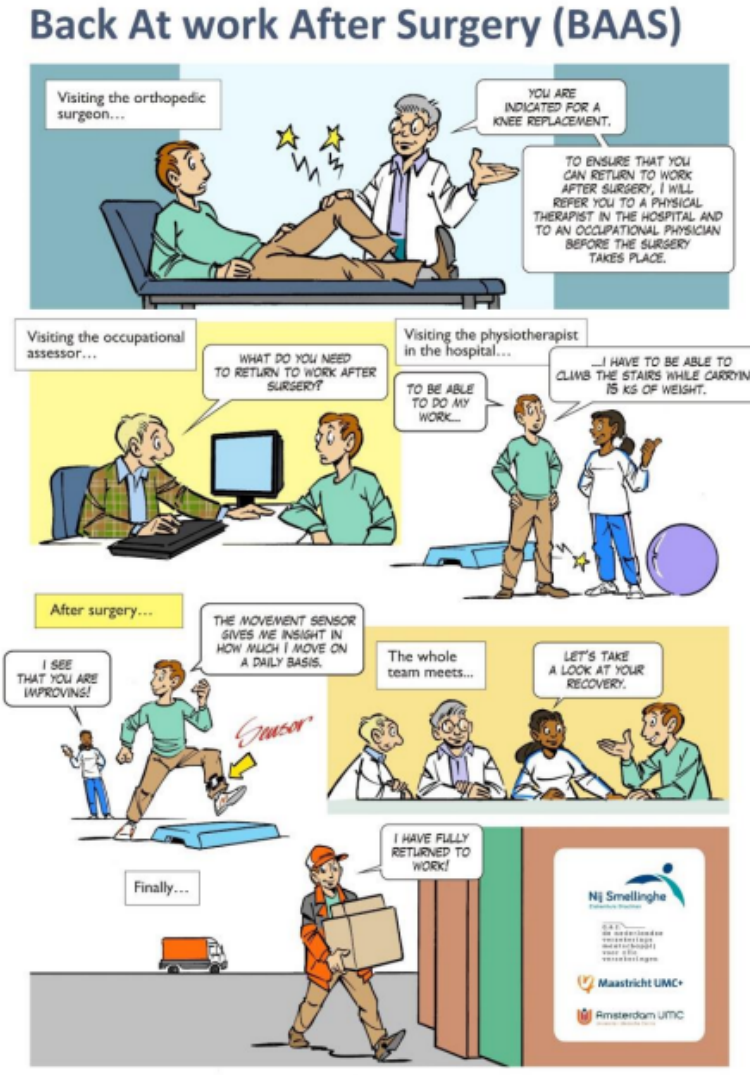

Figure 1: BAAS care pathway

The Association of Pain Assessment in Clinical Examination and MRI Findings in Acute Hamstring Injuries

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Objectives: 1） To compare patient-reported and palpation-identified pain locations with the primary injury site on Magnetic resonance imaging (MRI).

2） To examine the relationship between palpation pain length and edema length on MRI

Design: Cross-sectional study

Method: This cross-sectional study included patients with acute hamstring injuries. Maximal pain location was identified by (1) the patient (self-reported group) or (2) palpation during clinical examination (palpation-assessed group). A sports physician measured the proximal-to-distal length of palpation pain, and a radiologist identified the primary injury site and edema length on MRI. Distances between pain sites and injury locations were analyzed, and lengths of palpation pain and edema were compared using linear regression and Spearman's correlation.

Results: The study included 28 patients in the self-reported group and 53 in the palpation group. The palpation group showed a closer match to the primary injury site on MRI than the self-reported group ($p = 0.058$, 95% CI [0.02, 0.96], CLES = 0.615). Edema length was significantly greater than palpation pain length ($p < 0.001$, Cliff's Delta = 0.61, 95% CI [0.44, 0.74], CLES = 0.80). A weak correlation was found between palpation pain length and edema length (Spearman's $r = 0.22$, 95% CI [0.01, 0.41], $R^2 = 0.04$).

Conclusion*:* The location of maximal pain on palpation by a physician is more accurate than the patient's subjective report. The length of pain on palpation is shorter than oedema on MRI and they are only poorly correlated.

3. Sports/Health Sciences

Longitudinal change in physical activity components among community-dwelling older adults.

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Abstract

Introduction: Complexity of Physical Activity (PA) and health effects are not fully captured using common measures such as duration and intensity. Extending these measures with the PA components of strength, mechanical strain and turning actions might offer a more complete picture of PA in older adults. We explore the course and heterogeneity of the PA components over time.

Methods: Prospective data from the Longitudinal Aging Study Amsterdam cohort study (1992 – 2019) were used. We included all participants with at least one follow-up measure, resulting in a sample of N=5002. PA component scores of strength (range 1-4), mechanical strain (range 1-3), turning actions (range 1-3), intensity (range 2.5 – 6.5) were assigned to each self-reported activity. Duration was self-reported and recalculated into minutes/day (range 0-960). All five scores were categorized into tertiles. We applied Sequence Analysis to plot the trajectories of the PA components and Optimal Matching algorithms to identify groups with similar trajectories over time. Analyses were stratified for men and women to account for differences in PA behaviors.

Results: Our sample had a mean baseline age of 66 years (sd=8.6) and 52% were women. The mean follow-up time was 11.1 years (sd=8.5), and 22% of the respondents died during the 10-year follow-up. For the duration component, 119 distinct trajectories were identified over the 10-year follow-up. OM on these trajectories resulted into six clusters of similar trajectories: stable long, stable medium, stable short, decreasing duration, early deceased, late deceased.

Discussion: A solution of six clusters of similar trajectories could be fitted to all components for the 10-, 20-, and 30-year follow-up periods. However, PA component trajectories differed between components, as well as between sexes within the same component. These findings show that PA components have different trajectories over time, and the importance of these differences in association with health outcomes should be studied in future research.

Keywords: Strength, Intensity, Mechanical strain, Turning Actions

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Gait variability long-term after rotationplasty

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Introduction and purpose

Patients after rotationplasty achieve high functional outcomes. However, the impact of active ankle joint loss, a decrease in muscle volume and loss of proprioception on gait deviations and potential instability remains unknown. This study evaluates whether gait stability is reduced long-term after rotationplasty compared to healthy controls.

Method

Thirty patients, median age 47 years (IQR 43-51) with a median follow-up of 33 years (IQR 29-35), were eligible and participated. In this cross-sectional observational study, 3D-gait kinematics were captured with a 12-camera Vicon system at comfortable and a fixed walking speed (1.2 m/s). Gait stability was measured by the variability (standard deviation) of step width and the margin of stability (MoS) in the mediolateral (ML MoS) and anterior-posterior direction (AP MoS) for both the intact and amputated leg.

Results

At comfortable speed, rotationplasty patients walked slower than controls (1.18±0.1 vs 1.42±0.2, $p < 0.001$), with higher step width (215±40 vs 175±21 mm, $p < 0.001$) and larger step width variability (27±5 vs 19±4 mm, $p < 0.001$). ML MoS was 50% larger ($p < 0.001$) on the rotationplasty side and 25% larger ($p = 0.03$) on the intact side, while AP MoS was 16% ($p < 0.001$) and 17% smaller ($p < 0.001$) for the rotationplasty and intact sides, respectively. At fixed speed, rotationplasty patients had a higher step width (220±47 vs 175±18 mm, $p = 0.02$) and step width variability (26±6 vs 20±4 mm, $p = 0.02$). ML MoS was significantly higher 21% ($p = 0.03$) for the amputated side, but not for the intact side. No significant differences in AP MoS were found at fixed speed.

Conclusion

Step width, step width variability, and ML MoS on the amputated side were increased in rotationplasty patients at both speeds, while differences on the intact side were observed only at comfortable walking speed. Increased step width variability indicates higher fall risk and reduced gait stability. Rotationplasty patients compensated by increasing step width, mediolateral base of support and ML MoS.

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THE EFFECT OF HEAT ACCLIMATION ON CRITICAL ENVIRONMENTAL LIMITS AND RATE OF RECTAL TEMPERATURE CHANGE

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Introduction With global temperatures rising, the exposure of people executing physical demanding work to warm environments is increasing (1). Exposure to warm conditions reduces performance and increases heat-related injury risk (2). Heat acclimation (HA) is used to combat these negative outcomes (3). Limited evidence exists on the magnitude of HA-induced improvements in work capacity and the minimal time needed to achieve these improvements. As HA is a time consuming and a physically demanding endeavour, knowledge regarding the minimal time investment needed to reach work capacity improvements is warranted.

Purpose This study quantified the effect of HA on critical wet-bulb globe temperature ($WBGT_{crit}$) and rate of rectal temperature change (vT_{re}). Both measures can be used for developing guidelines with regards to occupational safety whilst working in warm environments.

Methods Twenty-eight non-acclimatized participants were divided into a HA (N=15) and control (CON; N=13) group. The HA-group underwent a warm-humid (35°C, 65% relative humidity) controlled hyperthermia HA protocol (5-9 days of achieving T_{re}~ 38.5°C for 60 min) and four progressive heat stress tests (HSTs) to identify $WBGT_{crit}$ and examine vT_{re}: pre-, after five and nine days of HA, and four-to-eight days of no heat exposure following HA. CON performed two HSTs at least two days apart without heat exposure in between.

Results HA increased $WBGT_{crit}$ after nine (28.5 ± 2.7°C vs. 30.5 ± 2.0°C; $P = 0.016$), but not five days (28.5 ± 2.4; $P > 0.05$). No effect of HA on vT_{re} was observed ($P > 0.05$). Four-to-eight days post-HA, $WBGT_{crit}$ ($P = 0.704$) and vT_{re} ($P = 0.079$) did not differ compared to nine days of HA. However, a workplace-relevant reduction in vT_{re} (-0.4 ± 0.3°C/ hour) was observed when comparing pre-HA to four-to-eight days post-HA.

Conclusion In conclusion, our results demonstrate that more than five days of HA are required to increase $WBGT_{crit}$ and indicate that nine days of HA proceeded by adequate recovery may reduce vT_{re} during exercise in the heat. These findings enhance our understanding of HA's effect on work capacity in the heat and may be used to design occupational guidelines.

1. **Vecellio DJ, Kong Q, Kenney WL, and Huber M**. Greatly enhanced risk to humans as a consequence of empirically determined lower moist heat stress tolerance. *Proc Natl Acad Sci U S A* 120: e2305427120, 2023.
2. **Periard JD, Eijsvogels TMH, and Daanen HAM**. Exercise under heat stress: thermoregulation, hydration, performance implications, and mitigation strategies. *Physiol Rev* 101: 1873-1979, 2021.
3. **Tyler CJ, Reeve T, Sieh N, and Cheung SS**. Effects of Heat Adaptation on Physiology, Perception, and Exercise Performance in the Heat: An Updated Meta-Analysis. *Journal of Science in Sport and Exercise* 2024.

THE COST-EFFECTIVENESS OF THE DUTCH IN BALANCE FALL PREVENTION INTERVENTION COMPARED TO EXERCISE RECOMMENDATIONS AMONG COMMUNITY-DWELLING OLDER ADULTS WITH AN INCREASED RISK OF FALLS: A RANDOMIZED CONTROLLED TRIAL

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Introduction Falls among older adults are a growing public health issue, and are associated with injuries and increased societal costs. Therefore, implementation of effective fall prevention interventions is important. Given limited healthcare resources, evaluating the cost-effectiveness of these interventions is essential.

Purpose We aimed to evaluate the cost-effectiveness of the In Balance fall prevention intervention for community-dwelling older adults with an increased risk of falls compared to general physical activity recommendations (control) from a societal perspective.

Methods An economic evaluation was conducted alongside a twelve month, single-blind, multicenter randomized controlled trial. Participants were 264 non- and pre-frail community-dwelling adults aged 65 years or older with an increased fall risk. We assessed costs from a societal perspective and effects included the number of falls, fall-related injuries, and Quality-Adjusted Life Years (QALYs) based on the EuroQol Five-level questionnaire (EQ-5D-5L) and the Adult Social Care Outcomes Toolkit (ASCOT). Missing data were handled using Multiple Imputation by Chained Equations. Incremental costs and effects were estimated using Seemingly Unrelated Regressions and used to estimate Incremental cost-effectiveness ratios (ICERs).

Results On average, In Balance was less expensive and more effective than control, but differences were not statistically significant. ICERs indicated dominance of the intervention for prevented falls (€-14,329 per prevented fall), prevented fall-related injuries (€-14,569 per prevented injury), and QALYs based on both the EQ-5D-5L (€-168,265 per QALY gained) and ASCOT (€-135,797 per QALY gained). The probability of cost-effectiveness of In Balance compared to control was 98% at a willingness to pay (WTP) of €0 per unit of effect gained.

Conclusions Based on this study, we conclude that In Balance may be considered cost-effective compared to control. Future research should explore whether In Balance as part of a comprehensive fall prevention strategy is cost-effective.

Markerless capture of gait kinematics while walking with ankle-foot orthoses

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Introduction

Markerless motion capture is an emerging technique for measuring gait kinematics without requiring trained personnel to place markers. This might provide an efficient way to evaluate effects of AFOs on gait, and tuning their properties. While markerless systems generally yield comparable sagittal gait kinematics to marker-based systems as shown in able-bodied individuals and patients with various disorders, larger errors between systems have been observed in AFO users. However, no study has controlled for shoes-only walking to isolate the effects of the AFO in either group.

Purpose

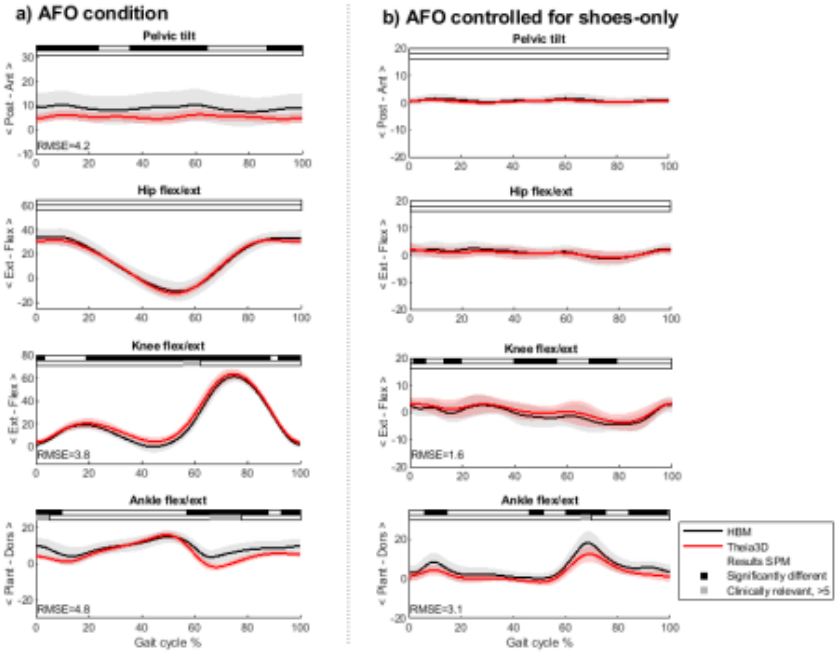
To investigate whether markerless motion capture produces different gait kinematics compared to a marker-based system in able-bodied individuals, with and without controlling for shoes-only walking?

Methods

Clinical gait analyses were performed in 15 adults (8 women, mean age 28±3) walking with shoes and dorsal leaf spring AFOs. Kinematics were captured using the Human Body Model (marker-based) and Theia3D (markerless) simultaneously. Statistical parametric mapping paired t-tests compared sagittal pelvis, hip, knee and ankle angles for the AFO condition, with and without controlling for their shoes-only data. Root mean square errors (RMSE>5^{o} were considered clinically relevant) were calculated for significant differences.

Results

Significant differences (p<0.05) were observed in pelvis, knee, and ankle angles during AFO walking, with RMSE≤4.8^{o}. Knee flexion was larger for the markerless system during 0-3%, 19-86%, and 92-100% of the gait cycle, while ankle dorsiflexion was smaller from 0-10%, 57-88%, and 92-100%. Controlling for shoes-only, significant differences (p<0.04) in knee and ankle angles remained, but RMSE were ≤3.1°.Knee angles were larger with the markerless system (at 1-6%, 13-20%, 40-56%, and 68-79%GC), and ankle angles were smaller (at 6-15%, 46-51% and 60-75%, and 84-99%GC).



Conclusion

This study in healthy individuals found significant differences between markerless and marker-based systems for sagittal pelvic, knee and ankle kinematics during AFO walking. Controlling for shoes-only gait reduced these differences, suggesting most discrepancies are unrelated to AFOs. Differences in ankle kinematics may result from foot movement within shoes. However, it is unknown which system most accurately measured the ankle angle. Further studies with various AFO types and patient populations are needed before clinical implementation.

FEEDBACK CONTROL INCREASES IN FASTER SPEED WALKING FOR GAIT STABILITY IN THE ANTERIOR-POSTERIOR DIRECTION

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Introduction

Gait stability requires control of the center of mass (COM) trajectory relative to the base of support, which is in part achieved by feedback based on sensory information. However, it is unclear if, and how, this feedback control changes with walking speed, as the contributions of different sensory systems have shown opposite variations across speeds.

Purpose

In this study, we applied a feedback model to investigate how walking speed affects feedback control of gait stability. In doing so, we focused on the anterior-posterior direction.

Method

15 healthy young subjects (21±4 yrs, 1.7±0.1m, 63±9kg; mean±SD) participated in this study. Subjects walked on a treadmill for 5 minutes at three different speeds: 2 km/h, 4.5 km/h, and 5.5 km/h, performed in a random order. Model fit and feedback parameters were estimated and compared.

Results

Our results showed good model fits with R^2 ranging from 0.52 to 0.81 across all subjects and speeds. Feedback delays decreased significantly with increasing speeds, with the delay during slow walking (69%±7% of the gait cycle), being significantly longer than in normal (64%±4%) and fast walking (61%±3%). The position gains were significantly larger during normal walking and fast walking, than during slow walking. The estimated velocity gains did not differ significantly between walking speeds.

Conclusion

Our results revealed a speed-dependent characteristic of feedback control of gait stability in the anterior-posterior direction. As walking speed increases, the estimated feedback delay decreased, while the position gain increased. The increased position gain indicates increased feedback involvement in fast walking, which may suggest a dominant role of somatosensory feedback in high-speed locomotion.

THE RELATIONSHIP BETWEEN WORKLOAD AND INJURIES IN DUTCH CROSSFIT ATHLETES; A PROSPECTIVE COHORT STUDY

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Introduction

CrossFit is a popular strength and conditioning program. Previous research indicated that changes in training load and experience level may be risk factors for injuries in CrossFit.

Purpose

This study aimed to 1) investigate injury incidence and 2) examine the association between changes in training load and injuries in Dutch CrossFit athletes.

Method

In this prospective cohort study, we recruited participants from affiliated CrossFit gyms throughout the Netherlands. Over a 12-week follow-up period, participants recorded each training session's duration and Rating of Perceived Exertion (RPE). Additionally, they completed the Oslo Sports Trauma Research Center Questionnaire on Health Problems weekly to assess the occurrence of injuries. We calculated injury incidence per 1,000 hours of exposure and assessed the longitudinal association between changes in training load (session RPE * session duration) and injuries using generalised estimating equations. We distinguished between any and substantial injuries and investigated effect modification for experience level and sex.

Results

A total of 152 participants (mean age: 33.2 ± 8.5 years; 51% female) were included, with 68% lost to follow-up by week 12. The injury incidence was 20.4/1,000 hours. We found no overall association between training load and injuries (Odd Ratio: 0.99, 95% confidence interval 0.96-1.01) when correcting for gender and experience level. However, we did find effect modification for experience level; for beginners (<6 months), higher training load increased injury risk (OR: 1.05, 95%CI: 1.01-1.09), while for intermediate athletes (6-24 months), lower training load increased injury risk (OR: 0.83, 95%CI: 0.77-0.89).

Conclusion

The injury incidence in the current study was higher than in previous studies, which may be attributed to our injury definition, which incorporated any injuries instead of time-loss injuries only. Furthermore, we did not find an overall association between training load and injuries in CrossFit athletes, but the effect of training load on injury risk appears to vary by experience level. Future studies should employ injury recording methods that capture all injuries rather than just time-loss injuries. Additionally, they should investigate the differences in response to training load for beginners, as they appear to be at higher risk for injury with changes in training load.

INJURY INCIDENCE AMONG BRAZILIAN JIU-JITSU PRACTITIONERS GLOBALLY: A CROSS-SECTIONAL STUDY IN 881 PARTICIPANTS

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Introduction
Brazilian Jiu-Jitsu (BJJ) is a rapidly growing martial art characterised by ground fighting and submission techniques. Injury incidence ranges from 9 per 1,000 matches in competition to 308 per 1,000 athlete years in training. The heterogeneity of injury definitions and incidence calculations makes comparing these data difficult. Injuries

Purpose
Despite its popularity, there is limited data concerning BJJ. Consequently, this study aimed to describe the incidence and characteristics of injuries in BJJ practitioners.

Methods
This retrospective survey targeted BJJ practitioners globally who trained at least once per week. The survey was distributed online and via physical posters at multiple Dutch BJJ competitions. Data collection took place from February 15th to March 17th, 2024. We collected training, competition, and injury data from the past 12 months. Complaints that required medical attention caused time loss (≥1 week) or led to training modification (≥2 weeks), were defined as injury.

Results
Out of 881 participants, 817 (90%) were male, the average age was 30.5 years (SD 8.6), and they trained for 6.8 hours (SD 5.2) per week. Injury information was gathered for a total of 886 injuries. The injury incidence was 5.5 (95% CI: 4.9 – 6.08) per 1000 training hours and 55.9 (95% CI: 38.8 – 73.0) injuries per 1000 matches. Most injuries (n=794, 89%) occurred during training, predominantly (n=624, 79%) during sparring. The knees (n=216, 25%) and shoulders (n=111, 13%) were the most commonly affected body regions (Figure 1). We discovered that participants with lower belt levels sustained more injuries than those with higher belt levels.

Conclusion
This study found an injury incidence of 5.5 per 1000 hours of training and 55.9 per 1000 matches for BJJ practitioners. Future preventative practices should focus on free sparring in training to enhance prevention efforts. Prospective studies on BJJ practitioners are also needed to understand injury aetiology better.

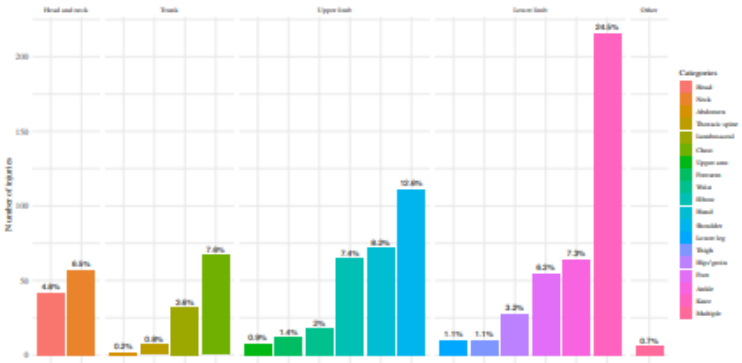

Figure 1: Number of injuries per body region

PLANTAR PRESSURE ANALYSIS OF INDOOR VERSUS REGULAR CUSTOM-MADE FOOTWEAR IN PEOPLE WITH DIABETES AT HIGH ULCER RISK

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Introduction Custom-made footwear specifically designed to use indoors increases adherence to prescription footwear in people with diabetes, peripheral neuropathy and high ulcer risk, compared to using only regular custom-made footwear. A pilot study showed similar maximum peak pressures with regular footwear, a quality requirement considering the indoor footwear replaces the regular footwear for indoor use. A more in-depth analysis of pressure distribution and gait stability of this indoor footwear is yet to be conducted. Such investigation can demonstrate if indoor footwear is a biomechanically safe replacement for regular footwear for indoor use.

Purpose The aim was to compare indoor and regular custom-made footwear for pressure distribution and gait stability in people with diabetes at high risk of ulceration.

Method Custom-made indoor footwear was provided to 36 participants with diabetes, peripheral neuropathy, and a recently healed plantar foot ulcer or (partial) foot amputation. All participants were in possession of regular pressure-optimized custom-made footwear, of which the last was used to design the indoor footwear. In-shoe plantar pressures were measured during walking in both shoe types, from which multiple peak plantar pressure and center-of-pressure parameters were calculated. Peak pressure parameters, including multidimensional parameters[1], defined offloading effectiveness, while center-of-pressure parameters defined foot roll-over and gait stability[2,3]. Paired t-tests were used to assess differences between footwear types, where statistical parametric was used in (multi)dimensional parameters.

Results A total of 132 shoes, 66 per footwear type, of 36 participants were analyzed. Outcomes for all peak pressure parameters were non-significantly higher in the indoor compared to regular footwear ($p>0.05$). Maximum average difference in the forefoot regions was 10.1 kPa for maximum peak pressure, 1.22 kPa.s for pressure time integral and 0.13 kPa/mm for the pressure gradient. Overall pressure distribution over time for all participants is shown in Fig.1. Both foot roll-over and stability center-of-pressure parameters were not significantly different between footwear types.

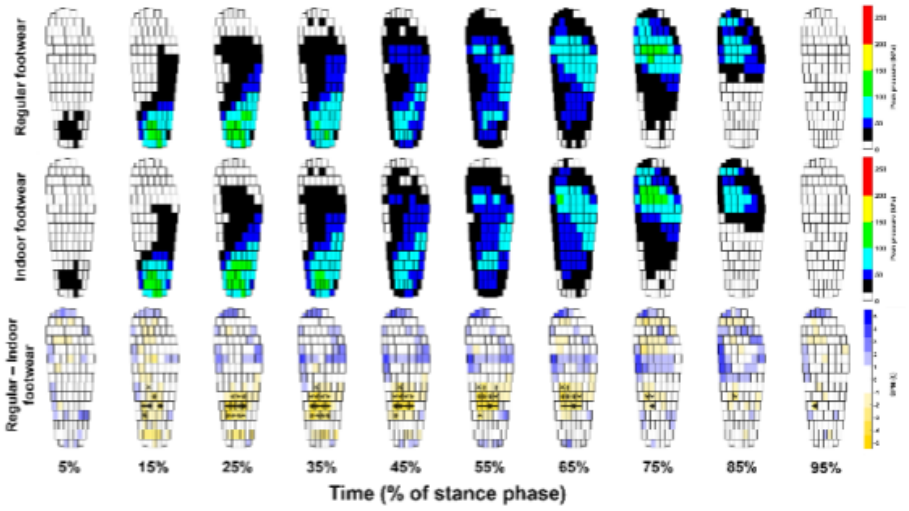

Fig.1: Peak plantar pressure distribution of regular and indoor custom-made footwear in a pressure time map. The bottom row shows the statistical comparison between both types of footwear. Blue = pressure regular > indoor footwear, yellow = pressure indoor > regular footwear.

Conclusion No significant differences were found in pressure distribution, foot roll-over and gait stability between footwear types. These results show that custom-made indoor footwear is a biomechanically safe alternative for use indoors to regular custom-made footwear in people with diabetes at high ulcer risk.

[1]Vossen et al. (2025). J. Biomech., 180: 112502.
[2]Menz et al. (2018). Gait Posture., 63: 91-96.
[3]Pol et al. (2021). Gait Posture., 88: 78-83.

BASELINE CLINICAL AND MRI VARIABLES ARE ASSOCIATIED WITH TIME TO RETURN TO PLAY FOLLOWING ACUTE HAMSTRING INJURY: A MULTICENTRE, PROSPECTIVE MERGED COHORT STUDY OF 324 INJURIES.

Milo J.K. Mokkenstorm,[1,2,3,4], Muhammad Ikhwan Zein,[1,2,3,4,7] Prof. Marco Cardinale [5] Louis Holzhausen,[5,8,9] Rodney Whiteley,[5] Robin Vermeulen,[2,5] Arnlaug Wangensteen,[5] Prof. Gino MMJ Kerkhoffs,[1,2,3,4] Gustaaf Reurink,[1,2,3,4] Prof. Johannes L. Tol,[2,3,4,5]; *GF Study group, HAR study group, HIR study group, HIT study group.*

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Abstract

Background: Following hamstring injury the athlete's foremost question is, 'when can I return to play?' To answer this question previous studies have investigated the association between potential predictive variables and time to return to play (RTP). The majority of these studies used univariate analysis, therefore the independent associations between these variables and time to RTP remains unknown.

Objectives: This study aimed to examine the independent associations between baseline clinical and radiologic variables with time to return to play following hamstring injury.

Methods: We merged data from four prospective studies conducted in Qatar and the Netherlands (three randomized controlled trials and one ongoing prospective cohort study). Inclusion criteria included athletes with MRI-confirmed hamstring injuries (<7 days). Two multivariable linear regression models were created. The first model included clinical baseline variables in the second model contained both radiologic variables were added.

Results: 324 athletes were included in the analysis. In the first model four variables were independently associated with time to RTP: Level of sports (professional athletes had a 30% CI 20-39% shorter time to RTP); type of sports (football players had a 15% CI 1-30% shorter time to RTP); length of pain during palpation (6% CI 0-12% longer time to RTP for every centimetre increase); and isometric strength of the injured leg in 15° knee flexion (2% CI 1-3% longer time to RTP for every 10 Newton increase) explaining 26.1% of variance in time to RTP. In the second model five variables were found to be independently associated with time to RTP: level of sports (professional athletes had a 36% CI 28-44% shorter time to RTP) type of sports (football players had a 19% CI 5-34% shorter time to RTP); isometric strength of the injured leg in 15° knee flexion (2% CI 1-3% longer time to RTP for every 10 newton increase); intramuscular tendon waviness (the presence of waviness was associated with 23% CI 7-41% longer time to RTP); length of intramuscular tendon disruption (3% CI 1-4% longer time to RTP per centimetre increase), explaining 33.2% of variance in time to RTP.

Conclusion: Our findings show that professional football players without intramuscular tendon waviness have the most favourable time to RTP prognosis

BASELINE CLINICAL AND MRI VARIABLES ARE ASSOCIATIED WITH TIME TO RETURN TO PLAY FOLLOWING ACUTE HAMSTRING INJURY: A MULTICENTRE, PROSPECTIVE MERGED COHORT STUDY OF 324 INJURIES.

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Conclusion: Our findings show that professional football players without intramuscular tendon waviness have the most favourable time to RTP prognosis

MECHANICAL EFFICIENCY DURING SUB-MAXIMAL CYCLING IS UNDERESTIMATED BECAUSE NEGATIVE MUSCULAR POWER IS IGNORED

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Introduction

Muscular mechanical efficiency has frequently been studied in sub-maximal cycling, using the average mechanical power output and the rates of oxygen consumption and carbon dioxide production. In this approach, it has implicitly been assumed that the average amount of positive muscular mechanical power equals the average mechanical power output, or in other words, that the average amount of negative mechanical muscular power is zero. It is currently unclear whether this assumption is true, and if not, how large the influence of negative muscular power would be on mechanical efficiency estimates during sub-maximal cycling.

Purpose

We first aimed to estimate the amount of negative mechanical muscular power during sub-maximal cycling at different combinations of cadence and average mechanical power output. We then used our estimates of the amount of negative muscular power to investigate the influence of negative muscular power on mechanical efficiency estimates.

Method

We identified muscle stimulations for a musculoskeletal model of a cyclist at different combinations of cadence (60-120RPM) and average mechanical power output (50-250W). The estimated amounts of negative muscular power were then used to correct gross efficiency values obtained from the literature for the effects of negative muscular power. This was done by subtracting the metabolic power consumed for negative muscular power from the experimentally measured metabolic power and by multiplying gross efficiency with the ratio between the average amount of positive muscular power and average mechanical power output.

Results

The amount of negative muscular power was substantial in all conditions, with the average across conditions being -84.6W (56.4%). Corrections for negative muscular power led to a substantial increase in gross efficiency, with the average increasing from 16.9% to 27.5%. In the literature, gross efficiency has been found to decrease with increasing cadence and increase with increasing average mechanical power output. After correcting for negative muscular power, both relationships disappeared.

Conclusion

Due to neglecting the influence of negative muscular power, current measures of in vivo muscular mechanical efficiency likely underestimate the true muscular mechanical efficiency during sub-maximal cycling.

MUSCLE SYNERGIES DURING WALKING: INFLUENCE OF TIME-POST STROKE AND METHODOLOGICAL CONSIDERATIONS

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Introduction:
Muscle synergies are defined as fixed patterns of muscle co-activation or a systematic coupling of muscle activation across joints. While healthy adults typically exhibit four to five synergies during walking, post-stroke individuals often present with fewer synergies, reflecting impaired primary motor control. However, the impact of time post-stroke and their clinical implications remains unclear with methodological inconsistencies across studies contributing to variability in findings.

Purpose:
This study investigates the effect of time post-stroke on the number of synergies and its clinical implications. Additionally, it tries to provide recommendations for standardizing muscle synergy analysis in post-stroke walking

Method:
A systematic literature search was conducted in Medline, Embase, and Web of Science (until 05/11/2024) to identify studies reporting muscle synergies during post-stroke walking. Extracted data included participant characteristics, walking parameters, muscles selection, EMG acquisition, and synergy extraction methods. A Chi-square test compared synergy prevalence between sub-acute (7 days to 6 months) and chronic (>6 months) phases after stroke, while Pearson's correlations examined its associations with walking speed and Fugl-Meyer Lower-Extremity scores.

Results:
A total of 23 studies (574 participants) were included, focusing on the chronic (12 studies) or sub-acute phase (6 studies) after stroke. Some studies included both phases (4 studies) or did not specify the phase (1 study). Participants in the sub-acute phase (N=73/88 [83.0%]) significantly ($p<0.001$) presented with fewer synergies compared to those in the chronic phase (N=123/211 [58.3%]). The intended correlation statistics were impossible due to underreporting of gait or clinical parameters and within-study heterogeneity. Therefore, recommendations to standardize muscle synergy analysis in post-stroke walking are mandatory. Analysis should compare the paretic, non-paretic, and control legs, include at least eight muscles, and use preferably non-negative matrix factorization (NNMF) with a variance accounted for (VAF) threshold of >90%. Since overground and treadmill walking at a self-selected speed showed comparable results both can be used.

Conclusion:
Fewer synergies were significantly associated with shorter time post-stroke. However, current evidence is insufficient to determine their impact on stroke recovery or gait characteristics. Standardizing muscle synergy analysis will improve studies comparability, enhance understanding of post-stroke motor control, and support phase-specific rehabilitation strategies.

Gait Adaptations Following Exercise-Induced Muscle Fatigue In Older Adults: Awareness and Intentionality

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Introduction

Exercise-induced muscle fatigue can affect gait behaviour, which can lead to an increased risk of falling in older adults. However, non-homogeneous changes in gait parameters indicate that older adults have different strategies to respond to exercise-induced fatigue. It remains unclear whether adaptations in gait parameters are a direct effect of exercise-induced fatigue or a compensatory strategy to counter (perceived) fatigue.

Purpose

To determine if older adults are aware of gait adaptations as a result of exercise-induced fatigue, if these adaptations are (un) intentional, and based on what information adaptations are executed.

Method

Eighteen healthy older adults (>65 year, 13 females) participated and performed walking trails (15m) while gradually becoming more fatigued by repetitive sit-to-stand exercises between the walking trails. Various gait parameters (i.e. step length, step width, gait speed, minimal foot clearance and margin of stability) were recorded with the use of THEIA Markerless Motion Capture. Directly after the walking trails participants were interviewed on their awareness and intentionality of gait adaptations when fatigued. Both objective and subjective data were used to check whether older adults' perceived gait adaptations were congruent with gait parameter data.

Results

Participants show a significant decrease in gait speed (-0.06m/s, p=.04) and increase in step width (+0.02m, p<.001) in the fatigued versus the non-fatigued walking trial. Step length, and the variability of both step length and step width showed no significant changes when comparing fatigued with non-fatigued walking trails. Furthermore, the majority of older participants are generally aware of adaptations in gait as a result of exercise-induced fatigue. Intentionality and whether the perceptions of adaptations were congruent with gait parameter data is currently analysed. This data will be presented at the AMS annual meeting.

Conclusion

Our preliminary conclusion is that the adaptations in gait might be individual responses to the fatiguing exercise which underlines the need for individual monitoring of potential fall-risk when older adults are fatigued.

OPTIMAL CONTROL MODELING REVEALS PERFORMANCE BENEFITS OF ANKLE IMMOBILITY IN CYCLING: IMPLICATIONS FOR PARA-CYCLING CLASSIFICATION

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Introduction The International Paralympic Committee (IPC) mandates the development of evidence-based classification systems for Paralympic sports, which minimize the impact of impairments on competition outcomes[1]. Ankle mobility is a key determinant for classification in C4 (e.g., unilateral ankle immobility) or C5 (e.g., mild to severely impaired unilateral ankle mobility)[2]. Para-cycling performance overlaps between C4 and C5[3]. Together, these factors suggest that ankle immobility may be classified incorrectly in the para-cycling classification system.

Purpose We investigated the potential impact of bilateral ankle immobility on cycling performance, quantified by the maximal average mechanical power output (AMPO) during one revolution.

Method We used a two-dimensional musculoskeletal model, comprising five rigid segments (representing crank, foot, shank, thigh and pelvis) connected by frictionless hinge joints and driven by nine Hill-type muscle-tendon-complex models (representing m. iliopsoas, m. rectus femoris, mm. vastii, m. gluteus maximus, bi-articular hamstring, mono-articular hamstring, m. gastrocnemius, m. soleus, and m. tibialis anterior; Fig.1)[4]. The nine optimal muscle activations over time were identified using an optimal control approach such that AMPO is maximized in two conditions: 1) bilateral ankle mobility, and 2) bilateral ankle immobility (fixed at 90°).

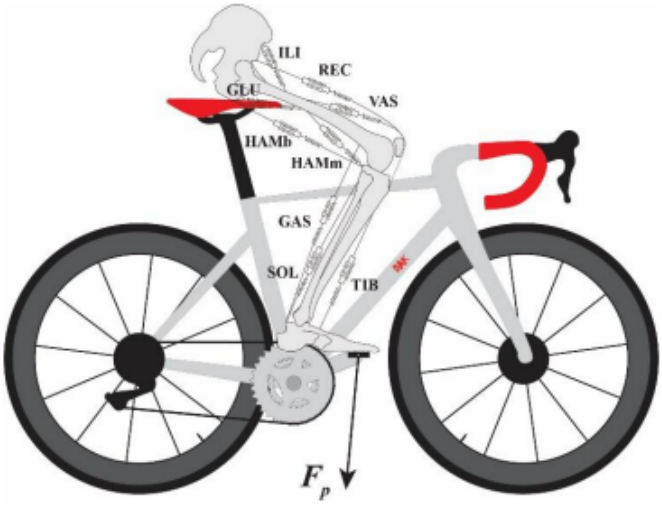

Figure 1. Cycling model

Results Our findings showed an 8% increase in maximal AMPO when cycling without (1122 W) versus with (1038 W) ankle mobility. This relative difference depends on the relative strengths of the leg muscles; doubling soleus strength caused a 5% decrease in maximal AMPO. These results may be explained by a trade-off between a decrement in power production by the plantar flexors with ankle immobilization and an increment in power production by other muscles because the immobilization mechanically solves a coordination problem[5].

Conclusion The model shows that bilateral ankle immobility may increase maximal AMPO. This might indicate that the current classification of this impairment should be revisited. We suggest careful testing of our model-based predictions through experiments.

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THE IMPACT OF VISUAL PERTURBATIONS ON BALANCE CONTROL DURING WALKING

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Introduction: Visual perturbations may lead to illusions of self-motion, affecting balance control during walking. We explored how people deal with different visual perturbations during walking by assessing foot placement and center of mass (CoM) states.

Purpose: Our aim is to investigate the relationship between the CoM state and foot placement when performing the aforementioned visual tasks during walking.

Methods: Here we conducted a walking experiment on younger adults to collect pelvis (as a proxy of the CoM) and foot kinematic data. There were three different visual tasks: normal walking (NW), tracking a moving target with head rotation (MT-HR), and fixating on a stationary target while the background moved (MB). Each visual perturbation included a moving and a stationary phase. Linear models were fit to the kinematics data to predict foot placement from CoM state at mid-swing.

Results: Over the whole trial, the presence of visual perturbations caused an increase in step width variability, foot placement residual error, and CoM position variability. During MT-HR perturbations, a significant right deviation of foot and CoM trajectories was observed in the stationary phase. Rightward foot placement errors were significant at the fourth, seventh, nineth and tenth step. During MB perturbations, a left deviation of foot and CoM trajectories was observed at the beginning of the moving phase. At the second, third, fourth, and sixth step, there was significant leftward foot placement error, while at the tenth step, there was a significant rightward foot placement error.

Conclusions: Visual perturbations hamper stabilization of walking. MT-HR led to deviations in the direction of the target, while MB caused a deviation opposite to the background movement. The response to the visual perturbations was delayed in MT-HR, while it was fast in MB. Opposite to our expectations, foot placement errors did not coincide with subsequent CoM deviations in the opposite direction. Apparently, foot placement errors were followed by stance phase adaptations moving the CoM in the same direction as the foot. This study enhances our understanding of the effects of visual perturbations on balance control during walking. Future studies will compare young and older adults.

PREDICTING PHYSICAL PERFORMANCE BEFORE AND AFTER TRAINING: INSIGHTS FROM MACHINE LEARNING USING SMALL SAMPLES

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Introduction: Research on performance optimization in sports remains challenging, due to the small samples and large individual variation in physiology and training adaptations. Machine learning (ML) solutions seem promising, but have not been tested for their capability to predict performance in this setting.

Purpose: The aim of this study was to predict 4-km cycling performance following a 12-week training intervention based on ML models with predictors from physiological profiling, individual training load and well-being, and to retrieve the most important predictors.

Methods: twenty-seven (out of 34 recruited) recreational cyclists were included in this study. Comprehensive physiological testing was performed at baseline, including 4-km time-trial performance, maximal oxygen uptake ($\dot{V}O_{2max}$), pulmonary $\dot{V}O_2$-kinetics, Wingate performance, vertical squat jump, 3D ultrasound imaging and anthropometry. Participants were randomly assigned to one of four distinct training programs. Adaptations were assessed post intervention. Cycling performance (expressed as mean power on the 4-km time-trial) was predicted at baseline, after training and for changes in performance using ML models (generalized linear models (*glm*), random forest (*rf*) and principal component regression (*pcr*) models). Specific techniques were applied to reduce the risk of overfitting, including train-test splits, hyperparameter tuning and prior selection of predictors. Model performance was assessed by R2 and mean absolute error (MAE).

Results: Cyclists completed the 4-km time trial with a mean power output of 4.1±0.7 W/kg. Changes in time-trial performance after training were not different between groups (P>0.05), but included substantial inter-individual differences. ML models predicted cycling performance with very strong model performance on unseen data before (R^2=0.875±0.060, mean absolute error (MAE)=0.260±0.061 W/kg using *glm*) and after training (R^2=0.792±0.100, MAE=0.266±0.084 W/kg using *glm*). However, changes in performance were less predictable (R^2=0.134±0.118, MAE=0.211±0.030 W/kg) [glm] or R^2=0.361±0.175, MAE=0.183±0.032 W/kg [rf]). Key predictors included power at V̇O2max, ventilatory thresholds, body composition, deoxygenation, sleep, and sickness.

Conclusion: ML models allow accurate predictions of cycling performance based on physiological profiling, individual training load and well-being during a 12-week training intervention, even using small sample sizes, although changes in cycling performance were more difficult to predict.

ARE MUSCLE PHENOTYPIC CHARACTERISTICS ASSOCIATED WITH RESPONSE TO EXERCISE TRAINING IN RHEUMATIC DISEASES AND SARCOPENIA?- A STUDY PROTOCOL

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Introduction In rheumatoid arthritis (RA) occurring muscle weakness, systemic inflammation may contribute to oxidative stress-induced mitochondrial dysfunction, impairing oxidative capacity and glucose metabolism. In contrast, muscle weakness in osteoarthritis (OA) and sarcopenia (SARC) may be linked to impaired protein synthesis. High-load (HL) resistance training may enhance myofibrillar protein synthesis, while low-load (LL) endurance training could improve oxidative capacity. This study examines muscle characteristics influencing exercise responses in OA, RA, and SARC patients.

Purpose This study explores intra-muscular pathways related to muscle plasticity, oxidative stress, energy production, and systemic inflammation to determine optimal exercise strategies for individuals with varying muscle phenotypes. We hypothesize that patients with lower muscle strength will respond differently to HL-resistance and LL-endurance exercises based on their condition.

Method A two-arm parallel-group exploratory trial includes 69 patients (23 OA, 23 RA, 23 SARC). Participants will be randomized into HL (n=34) or LL (n=35) groups using minimization for balance across important stratification factors, i.e., disease and gender. The 8-week intervention, performed three weekly using the Reforter device, aims to improve isokinetic muscle strength (primary outcome). Secondary outcomes include endurance, mitochondrial function, gene and protein expression, histology, and systemic inflammation. Muscle biopsies will assess pathways related to hypertrophy, atrophy, oxidative stress, and energy metabolism, while 3D ultrasound evaluates muscle morphology.

Results The study will compare changes in isokinetic muscle strength across patient groups before and after HL and LL interventions. Results will identify differential exercise responses and their correlations with biomarkers linked to muscle plasticity, oxidative stress, energy production, and systemic inflammation.

Conclusion This study will explore the effectiveness of different exercise interventions in each group of patients with distinct clinical diagnoses associated with muscle weakness by analyzing muscle tissue histology, gene and protein expression, mitochondrial function, and systemic inflammation. We will identify intra-muscular pathways related to muscle plasticity, oxidative stress, and energy production. Finally, the results will support to develop effective exercise protocols in OA, RA, and SARC patients.

PULMONARY AND EXERCISE CHARACTERISTICS OF COVID-19 PATIENTS WITH PERSISTENT EXERTIONAL DYSPNOEA AND/OR EXERCISE INTOLERANCE.

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Introduction During the pandemic, Dutch Sports Medicine departments saw a rise in patients with (suspected) COVID-19 reporting persisting exercise intolerance and exertional dyspnoea. However, objective data on the prognosis, symptom duration and return to sport (RTS) were lacking.

Purpose This study aimed to characterise pulmonary and exercise profiles by assessing VO_2max, ACSM exercise tolerance norms, symptom severity, and underlying cardiopulmonary pathologies.

Method This prospective case series was conducted in a large general hospital in the Netherlands, where standard care was provided. Patients were included if they had a suspected or confirmed COVID-19 infection from march 2020 on; experienced emerging or persisting exercise intolerance and/or exertional dyspnoea lacking other confirmed diagnoses that account for these symptoms; were at least 16 years of age, participating in sports at least once a week; and having performed a CPET. Data was collected during an initial consultation with a CPET, spirometry and clinical investigations, a 6-9 months follow-up consultation with CPET and spirometry and a long-term telephonic survey. Descriptive statistics and multivariate regression analyses were performed.

Results 34 participants were included, 52.9% were women, median age was 35 years with an IQR of 30 to 43.3 years, the median BMI was 23.8 kg/m2 with an IQR of 22.4 to 25.6 kg/m2. The median VO_2max was 36.5 mL/kg/min with an IQR of 29.0 to 41.7 mL/kg/min. The resulting ACSM norms had a median of the 61th percentile and an IQR of 33rd to 87th percentile. Few cardiopulmonary pathologies were identified; four patients required treatment for obstructive pulmonary function. Long-term follow-up showed that 62% of participants had negligible to no persisting exercise intolerance and 79% had negligible to no persisting exertional dyspnoea. However, only 52% of the participants had a RTS at a similar or better level. No significant predictors were found for long-term outcomes.

Conclusion Participants' VO_2max and ACSM norms fell within normal ranges, identified underlying cardiopulmonary pathologies were minimal. However, persistent symptoms remained present after 4 years and RTS rates were insufficient: highlighting key areas for clinical focus.

Periodic relations of separate physiological systems during intermittent exercise in different states

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Introduction

At the start of exercise, every individual, both athlete and patient, builds up a level of oxygen deficit. The level of oxygen deficit depends on how fast the body can adapt to the new physiological state, which is expressed in the time-constant $\tau_{V'O2}$. A greater $\tau_{V'O2}$ represents slow V'O2 kinetics and thus a longer adaptation time, depending on the delay caused by for example O_2-diffusion, circulation and O_2-consumption in the muscles. However, to what extent these processes contribute to $\tau_{V'O2}$ remains unclear.

Purpose

The purpose of this research is to study the phase and gain differences of different physiological systems during intermittent exercise in order to determine the influence of these systems to $\tau_{V'O2}$.

Methods

Ten healthy individuals performed four interval tests each consisting of 6x 1,5 minute of loaded and unloaded exercise, during which V'O2, CO_2, tidal volume, breathing rate and heart rate were measured. Each test was performed in either supine or upright position and either at moderate or high workload (respectively, 90% of Gas exchange threshold (GET) or GET+(0.2*V'O2max-GET)).

The intermittent exercise resulted in periodic fluctuation of the measured parameters. This allows to calculate the periodic relations (gain and phase) of these signals in MATLAB (R2023b, Mathworks inc.) after synchronization with a cross-correlation algorithm. The change of these time relations with different position or higher load tells us how they contribute to $\tau_{V'O2}$.

Results

The gain and phase difference of most cardiopulmonary parameters didn't change with the exercise tests at a higher load or in a different position. The most notable change is the slightly but significantly increased phase difference between heart rate and V'O2 when comparing moderate and heavy exercise (-6° vs -12°, p=0.09 (upright), 0° vs -7°, p=0.09 (supine)), indicating a greater $\tau_{V'O2}$ and thus a higher level of oxygen deficit.

Conclusion

The kinetics of the cardiopulmonary system seem stable among different workloads and body position. Taking the observed phase shift between heart rate and V'O2 into account, this allows for good estimations of the oxygen deficit and $\tau_{V'O2}$ at heavy exercise based on the cardiopulmonary kinetics at moderate level exercise.

REDUCING POSITIVE MUSCLE FIBER WORK IN SIMULATED WALKING: WHEN TO START?

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Introduction Exoskeletons providing a plantar flexion moment around the ankle joint can reduce metabolic energy consumption during gait[1], but not when actuation starts early during stance[2]. This might be because providing assistance during early and mid-stance causes less Achilles tendon stretch and greater muscle fiber excursion[3]. This leads to less contribution of the Achilles tendon recoil to the ankle moment during push-off, meaning that muscle fibers have to provide more metabolically costly positive work. Furthermore, the muscle fibers need to shorten from longer lengths, increasing shortening velocity and thus decreasing force generating capacity of the fibers.

Purpose Our aim was to use musculoskeletal modelling to investigate whether an assistance profile that only assists plantar flexion moment during muscle fiber shortening leads to less reduction in Achilles tendon stretch and, as a result, to more reduction in muscle fiber power than an assistance profile that also assists during muscle fiber lengthening.

Methods Soleus and tibialis anterior muscle tendon lengths and moment arms were computed from kinematics from Afschrift et al[4] using the Gait2392 model in OpenSim, and were used as input to an optimization in CasADi[5]. Muscles were described as Hill-type muscles, according to De Groote et al[6]. The total moment (soleus + tibialis anterior + exoskeleton) was set to be equal to inverse dynamics moment. We aimed to find excitations for which muscle activation was minimal, in three conditions:

- NoExo: no exoskeleton moment;
- PercID: exoskeleton moment as a percentage of inverse dynamics moment;
- ShortPercID: exoskeleton moment as a percentage of inverse dynamics moment, but only active when soleus fibers are shortening.

We compared soleus muscle fiber and Achilles tendon lengths and positive soleus fiber power and work for the three conditions.

Results As expected, PercID led to a decrease in Achilles tendon stretch and an increase in muscle fiber length compared to NoExo. For ShortPercID, Achilles tendon stretch and muscle fiber length were similar to NoExo (**Fig. 1**). Both assistance profiles decreased positive soleus fiber power (**Fig. 1**). As a result, soleus positive mechanical work decreased from 23.7J (NoExo) to 14.3J (PercID) and 13.3J (ShortPercID). Exoskeleton positive mechanical work was lower for ShortPercID (2.6J) than for PercID (3.3J).

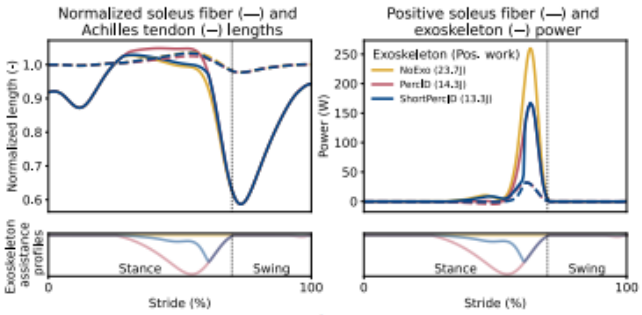

Figure 1: Normalized soleus fiber and Achilles tendon lengths (top left) and positive soleus fiber and exoskeleton power (top right) over a stride, and exoskeleton assistance profiles (bottom). Positive mechanical work delivered by soleus fiber for each condition is shown between brackets in the top right panel.

Conclusions Both exoskeleton plantar flexion assistance profiles based on the inverse dynamics moment led to a reduction in positive soleus fiber work. When only providing assistance during soleus fiber shortening, there was less decrease in Achilles tendon stretch, and with that more reduction in soleus muscle fiber positive work, even though less exoskeleton work was generated.

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MAXIMZING AVERAGE MUSCLE POWER REQUIRES MORE SHORTENING THAN LENGTHENING TIME

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Introduction: Maximizing average mechanical power output (*AMPO*) of periodic muscle contractions is critical for various species, but little is known about the optimal muscle contractile conditions in order to maximize *AMPO*. For example, at what frequency should the muscles shorten and lengthen for maximal *AMPO*? With which amplitude? Do these factors interact, and if so, how? Our study aims to answer these questions.

Purpose: To understand the relationship between periodic muscle shortening-lengthening and the maximal attainable *AMPO* for rat gastrocnemius medialis muscle.

Method: We combined physiological experiments with Hill-type muscle modelling to explore a wide range of muscle contractile conditions. First, we performed experiments to estimate the properties of gastrocnemius medialis muscle of each rat. Second, we performed various stretch-shortening cycles with substantial differences in the contraction parameters: cycle frequency (*CF*), *FTS* (fraction of the cycle time spent shortening; an *FTS* 0.35 indicates that *MTC* is shortening 35% of the cycle time), and *MTC* length amplitude (*AMP*). Third, we used a Hill-type muscle model, to provide insight in the relation between these contraction parameters and the maximal attainable *AMPO*.

Results: In the experiment, highest *AMPO* was found at a cycle frequency of 3 Hz, a *FTS* of 0.8 and a *MTC* length amplitude of 4 mm. Because measured and predicted *AMPO* correlated extremely well (R^2>0.98), we used the model to further explore the effect on contractile conditions on *AMPO* (Fig. 1). Predicted *AMPO* peaked at ~3 Hz, a *FTS* of ~0.87 and a *MTC* length amplitude of ~4.5 mm (Fig. 2). Notably, a wide range of contractile conditions yielded *AMPO* values close to the peak value (Fig. 1). The optimal cycle frequency and *MTC* length amplitude substantially interacted across various contraction conditions in order to maximize *AMPO*. On the other hand, the optimal *FTS* remained relatively constant across all cycle frequencies and *MTC* length amplitudes studied.

Conclusion: For maximal AMPO, rat gastrocnemius medialis muscle should spent substantially more time shortening than lengthening, independent of cycle frequency and *MTC* amplitude. This enhances *AMPO* by >50% compared to equal shortening and lengthening time at the optimal cycle frequency and *MTC* amplitude.

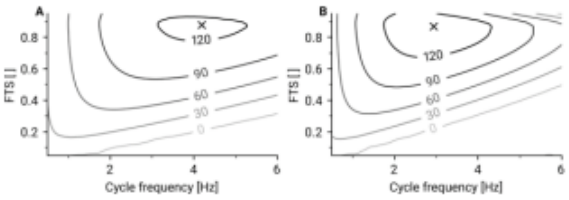

Figure 1: Predictions of maximal *AMPO* (depicted by contour lines) as a function of cycle frequency and *FTS* at a *MTC* amplitude of 3 mm (A) and 5 mm (B).

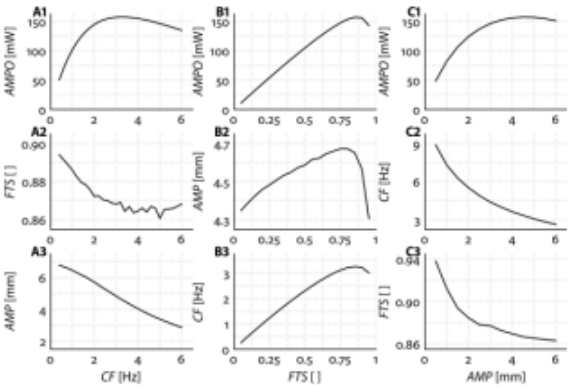

Figure 2: 3x3 grid of plots examining the interrelationship between contractile conditions – cycle frequency (*CF*), *FTS* and *MTC* amplitude (*AMP*) - and *AMPO*. For each column, one contractile condition was imposed, while optimizing the other two to maximize *AMPO*. Column 1) Imposed *CF*, optimal value of *FTS* (A2) and *AMP* (A3) to maximize *AMPO* (A1). Column 2) Imposed *FTS*, optimal value of *AMP* (B2) and CF (B3) to maximize *AMPO* (B1). Column 3) Imposed *AMP*, optimal value of *CF* (C2) and FTS (C3) to maximize *AMPO* (C1).

AVERAGE POWER OUTPUT OF QUADRICEPS FEMORIS AS A FUNCTION OF MOVEMENT PARAMETERS; EXPERIMENTS AND MODEL PREDICTIONS

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Introduction: Average mechanical power output (*AMPO*) is critical for performance in motor activities, but little is known about the relation between movement parameters and attainable *AMPO*. For example, how do movement frequency, movement amplitude and the ratio of shortening vs. lengthening time affect the maximal attainable *AMPO*? Do these factors interact, and if so, how?

Purpose: To explore the effect of movement parameters on the maximal attainable *AMPO* of human quadriceps femoris, using a combination of *in vivo* experiments and Hill-type muscle modelling.

Method: A 1D Hill-type muscle-tendon-complex (*MTC*) model represented the quadriceps femoris. Maximal attainable *AMPO* was predicted for various periodic knee joint movements, parametrized by cycle frequency, shortening:lengthening ratio (S:L ratio, 3:1 means that *MTC* shortens 75% of the cycle time) and knee joint amplitude. Based on these predictions (see Fig. 1A), we selected nine clear testable conditions. One subset was predicted to yield identical maximal attainable *AMPO* (Fig. 1A, red dots), while another subset was predicted to yield substantial differences in maximal attainable *AMPO*. (Fig. 1A, different colored dots). In the experiment, periodic knee joint movement were fully imposed by a knee dynamometer and participants received feedback on their cumulative mechanical work per cycle. Experimentally measured *AMPO* was z-score normalized for each participant individually and compared to those predicted in order to evaluate whether the model could accurately predict the influence of movement parameters on the maximal attainable *AMPO*.

Results: Measured *AMPO* and predicted *AMPO* correlated very well (R^2=0.95; see Fig. 1B). Therefore, we concluded that the model could accurately predict the influence of movement parameters on the maximal attainable *AMPO*. Predicted *AMPO* peaked at a cycle frequency of ~1.6 Hz, S:L ratio of ~3:1, and knee joint amplitude of ~50°. While cycle frequency and knee joint amplitude substantially interacted to maximize *AMPO*, S:L ratio was relatively constant across all cycle frequencies and amplitudes studied.

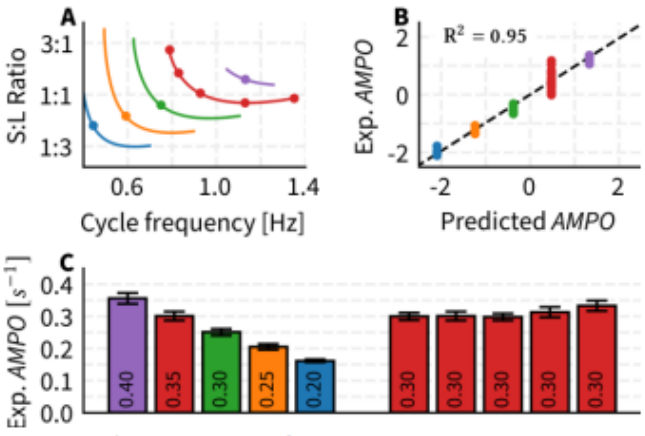

Figure 1: A) Contour lines of predicted maximal attainable AMPO for different cycle frequency and S:L ratios, only shown for experimentally feasible combinations. Solid dots represent conditions tested experimentally. B) Experimentally measured *AMPO* vs. predicted maximal *AMPO*, normalized to z-scores. C) Experimentally measured *AMPO* of participants, normalized to the product of *CE* optimum length and maximal isometric *CE* force for each participant. The value in the barplot depicts the predicted value.

Conclusion: Our experimental results were very accurately predicted by our Hill-type *MTC* model, indicating that we could accurately predict the effect of movement parameters on the maximal attainable *AMPO*. We predict that, in order to maximize *AMPO*, quadriceps femoris should spend more time shortening than lengthening (at a ratio of approximately 3:1) and should shorten-and-lengthen over a substantial distance (optimal at a knee range of motion of approximately 100°).

DO VARIATIONAL AUTOENCODERS DETECT THE UNDERLYING GAIT PATTERNS FROM DATA INDEPENDENT OF THE ACQUISITION TECHNOLOGY?

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Introduction

Gait analysis is crucial in rehabilitation for evaluating treatments and tracking progress[1,2]. Joint angle assessment, a key aspect of clinical gait analysis[3], generates large datasets, driving interest in Artificial Intelligence (AI) solutions. AI algorithms often require extensive data, motivating combining multiple datasets stemming e.g. from optical motion capture (OMC) or inertial measurement units (IMU)[4,5]. However, IMU data naturally contains higher noise levels[6] making the compatibility to OMC data questionable. Luckily, deep learning models like Variational Autoencoders (VAEs) excel at extracting key features in noisy data, which might enable data fusion despite the differences. Therefore, this study investigates the reliability of the intraparticipant latent space to assess the feasibility of combining OMC- and IMU-derived joint angle data for future analyses.

Methods The 3D lower-limb joint angles during treadmill walking of 12 able bodies participants (24.5 ± 4.5 years) were derived from IMU and OMC. The joint angle data was segmented into four second windows and presented as input data to a VAE pretrained on joint angles from 29 stroke survivors and 42 healthy participants[7]. To test the level of agreement, Bland Altmann statistics were calculated for the 3 latent features.

Results: Bland-Altman analysis showed high agreement between IMU and OMC data, with no systematic bias (Figure 1B). Visual inspection confirmed that data within the same participant and speed align in the latent space (Figure 1A), indicating the VAE identified the same gait patterns from both datasets.

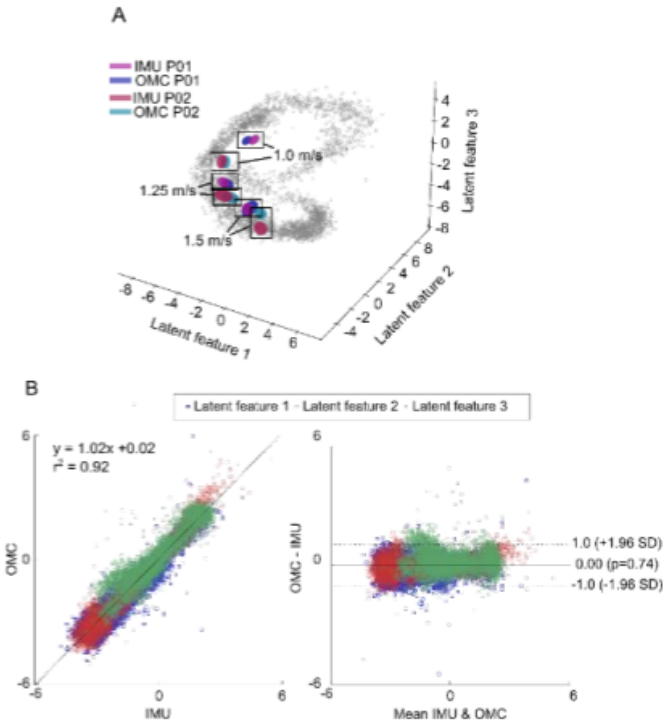

Figure 1: A) *Visual representation of the latent space, with two participants' data clusters, separated into the IMU and OMC data for each of the 3 speeds. Grey circles: original test data.* ***B)*** *The Bland Altmann plot with a linear regression to access the agreement between the 2 systems*

Conclusion: The VAE effectively extracts individual gait patterns regardless of the data collection system, enabling future data fusion across clinical sources. This approach can be expanded to other systems like 2D video or markerless motion capture. This may enable the use of AI in clinical settings, supporting objective diagnostic and monitoring of patients.

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