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Preventing Muscle Wasting During Rheumatoid Arthritis Flares: A Randomised Controlled Trial

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Background and Summary

This study aims to investigate aspects of muscle health changes following a disease flare-up in people with Rheumatoid Arthritis (RA) and test potential interventions to minimise any such changes.

RA is the most common inflammatory arthritis manifesting mainly as joint swelling and pain, limiting mobility, and eventually leading to loss of functional capacity. RA also has severe extra-articular manifestations (Bonfiglioli et al., 2023), affecting several tissues in the body including skeletal muscle (Farrow et al., 2021). People living with RA often present with an adverse body composition profile compared to the general population, characterised by low muscle mass at the presence of unchanged or even increased overall weight (Stavropoulos-Kalinoglou et al., 2007). This condition, termed Rheumatoid Cachexia, may affect up to 2 out of 3 people with RA and associates with active disease, further reductions in mobility, and low quality of life (Efthymiou et al., 2022).

While rheumatoid cachexia has been studied extensively, the course of its development, as well as potential causes or contributors to it are poorly understood. Inflammation, (Ollewagen et al., 2021) as well as lifestyle factors, such as energy intake, physical activity, or medication may contribute to the observed body composition changes (Masuko, 2014).

People living with RA often experience flares of disease activity, where high levels of inflammation, cause an acute exaggeration of symptoms, leading to very low levels of mobility. This is commonly treated with short-term steroid therapy which will rapidly reduce inflammation and allow the patient to regain mobility. However, that short period of high inflammatory load and low mobility may acutely affect muscle characteristics. Indeed, critically ill patients may lose up to 2% of skeletal muscle per day during the first week of hospitalisation. (Fazzini et al., 2023). This rapid decline in muscle health has been recently termed Acute sarcopenia (AS) by the European working group in sarcopenia and older persons (EWGSOP) (Cruz-Jentoft et al., 2019). Furthermore, recent work within our team is currently under review (Aldrich et al., 2023 *under review*) demonstrating the rapid decline of muscle mass and quality in people suffering with various diseases. Additionally, corticosteroids themselves may further contribute to muscle wasting in RA (Lemmey et al., 2018). Yet, the acute effects of flares and their treatment on muscle health in people with RA are not known.

Acute deterioration of muscle health following a flare may point towards a stepwise development of rheumatoid cachexia, i.e., bouts of acute deterioration that accumulate over time in steps rather than a continuous slow loss – which is the current understanding for the development of sarcopenia, the age-related muscle wasting. This would allow for target and potentially short-term interventions that could limit or even reverse muscle deterioration during a flare and help people with RA better maintain their functionality.

Exercise, and particularly resistance, is the most effective way to increase muscle mass, strength, and quality. However, people during and shortly after a flare may not be willing to

engage in such an intervention. Additional complexities around gym or home-based delivery, familiarisation, and safe execution render this a complex intervention with potentially limited applicability.

Nutritional supplementation on the other hand, is readily available, relatively cheap, and easy to administer. Specifically, for muscle health, amino acid supplementation, and particularly with leucine, has been shown to improve muscle mass and muscle function in older men and women (Ispoglou et al., 2016). Moreover, we have shown that amino acid supplements do not suppress appetite, are well tolerated and easy to consume. Finally, recent unpublished data from our lab suggest that amino acid concentrations in the blood following consumption alongside a meal remain elevated vs placebo for over 2 hours. This indicates that consuming two supplements per day would provide sufficient amino acids to induce beneficial effects on muscle health.

Therefore, the aims of our investigation are:

1. To understand the effects of acute RA flares on muscle health
2. To assess the efficacy of amino acid supplementation vs. standard care in maintaining muscle health.

Methodology

Participants

Eligible participants for this research study are people with rheumatoid arthritis who are experiencing a flare up of the condition. Inclusion and exclusion criteria are below.

Inclusion criteria:

RA patients who have either recently experienced a flare-up and contacted either the Rheumatology Helpline or were seen in one of the relevant clinics at Leeds Teaching Hospital Trust. The call/consultation should have occurred within the previous 4 days. Treatment for the flare may or may not have been administered already. If recruitment cannot be achieved within 4 days, we will allow up to 7 days for the baseline testing to take place before participants are no longer eligible.

Exclusion criteria:

Patients will be excluded if they present with any other comorbidity which affects muscle wasting, such as cancer or fibromyalgia, for example, or if they have had joint replacement surgery within the last 6 months. Also, patients with known or diagnosed kidney conditions will not be allowed to take part. Patients who are taking part in other research projects providing either pharmaceutical, nutritional or physical interventions will not be permitted to take part in this research project due to potential confounding variables and lack of control over participant behaviours. Patients who are pregnant will also be excluded from the study. Patients who are unable to provide their own informed consent will also be excluded. Patients who are unable to speak or understand English will also be excluded due to the need to read

and complete questionnaires written in English. Any participants who have a diagnosis of dementia or Alzheimer's disease will be excluded based on the requirement of dietary recall and remembering to take the supplement twice daily if in the intervention group. Disabled persons relying on wheelchair access will be excluded from the study due to the requirement of functional tests.

Procedure

The observation period of the research will consist of up to 5 visits to the laboratory at the Carnegie School of over a period of 3 months. Travel expenses will be reimbursed in the form of shopping vouchers from the research budget funding the study. In the event of some participants not being digitally literate and unable to receive vouchers, other means will be arranged with the participant to ensure they receive the reimbursement. The first visit to the laboratory will require the participants to recall all food and fluids consumed in the last 24 hours. Participants will be asked to refrain from strenuous physical activity 24 hours prior to each testing session and caffeine and alcohol from the evening before each testing session. Participants will also be required to arrive on all sessions having not eaten for >2 hours prior. Disease activity score will be assessed in each testing session (DAS-28).

The following schedule will be implemented throughout the period of participation and details of each session will be provided below:

1. First visit to Carnegie School of Sport for baseline testing (as soon as possible after flare diagnosis but no later than 7 days after)

2. 1-week post-baseline testing.

3. 2-weeks post-baseline testing.

4. 4 weeks post-baseline testing.

5. 12-weeks post baseline testing.

Participants will be randomised to either an amino acid supplement or standard care during the baseline testing session. The standard care is prescribed by the nurse at the hospital. The intervention group will be given supply for 2 supplements per day (one before breakfast and one before lunch) for a 4-week period following the baseline testing and familiarisation session. The supplements are already developed and paid for and in storage ready to use for research purposes.

Baseline Testing

<u>Anthropometry and body composition</u>

Height and weight will be assessed using standardised laboratory procedures and equipment including a bioelectrical impedance (BIA) machine (Seca mBCA 515 Body Composition Analyzer; a scale that also assessed body water content and estimates body composition).

Body composition will also be assessed using dual energy X-ray absorptiometry (DXA) scans. Participants will be asked to lay on the scanner with minimal clothing. DXA uses very low

intensity radiation to determine body composition and bone mineral density. It is commonly used in research and clinical practice and is considered a golden standard assessment tool for body composition and bone analysis while also being safe. Results will include information concerning lean tissue mass, fat mass, fat free mass and bone mineral density. However, only the first (baseline) and last (12-week). This takes approximately 30 minutes to complete.

Muscle mass and quality

Ultrasound (US) analysis of the quadriceps (vastus lateralis and rectus femoris) will be completed by a trained researcher and analysis will be obtained of muscle thickness, pennation angle, muscle cross-sectional area and muscle echogenicity. This will take approximately 20-30 minutes to complete. As part of the BIA assessment, this will also automatically offer another assessment of muscle quality.

Bloods

A trained phlebotomist will then take blood samples via venepuncture. 20ml of blood will be obtained in 5 tubes for subsequent assessment of:

- Amino acid content (8ml lithium heparin vacutainer tubes)

- Steroid hormone and Vitamin D content (1 x 10ml EDTA vacutainer tube)

- Erythrocyte Sedimentation Rate (2ml)

This stage will take approximately 5 minutes to complete.

Questionnaires

Participants will then be invited to relax for thirty-minutes, and enjoy a snack and a drink prior to muscle function testing, should they desire. During this break, participants will be given a series of questionnaires to complete which will offer an insight into the disease status of RA, the typical physical activity levels of the participants, the physical activity completed in the previous week, numerous diet recalls, and an overall quality of life questionnaire. The specific questionnaires included will be as follows:

- Medication Questionnaire/Record

- IPAQ (International Physical Activity Questionnaire - Short)

- 24-Hour Diet Recall

- RAQoL (Rheumatoid Arthritis Quality of Life)

- PROMIS (Patient-Reported Outcomes Measurement Information System)

- MUST (Malnutrition Universal Screening Tool)

RA disease activity will be assessed by using the Disease Activity Score 28 (DAS-28) questionnaire and assessing erythrocyte sedimentation rate. This questionnaire involves the palpation of joints and whether there is any pain or tenderness.

Muscle strength and function

Muscle strength and function testing will include the following:

- Hand grip strength (HGS) using a hand-held dynamometer to assess upper-limb strength. This will be assessed on both the dominant and non-dominant side. The participant will be asked to sit down and squeeze the dynamometer as hard as possible while their elbow is flexed at 90 degrees. This will be repeated twice on each arm and the highest score will be recorded.

- Knee extensor strength (KES) using a leg extensor to assess lower limb strength. Participants will complete a submaximal strength test following a 4-6 repetition max (RM) protocol. The score achieved will be recorded and converted in to a 1RM score using a validated prediction equation (Dohoney et al., 2002). Patients will first complete a series of warm-up sets at a lower weight. The 4-6RM will be determined within 4 sets with 3-5 minutes between sets. The initial weight will represent 50% of the patients perceived 4-6RM, after which the weight will be increased by 2.5-20kg per set until the patient fails to complete the selected repetitions. The final weight lifted successfully for 4-6 repetitions will be recorded as the 4-6RM.

- Muscle function tests incorporated in the short physical performance battery (SPPB) will be conducted. These tests include the 5 times chair to stand test (CST) in which the participant will be asked to stand from a seated position 5 times and the time will be recorded, the gait speed test (GST) which will assess walking speed over a 2.44 metre distance, and a balance test. The timed up and go test (TUG) and the 6 minute walk test (6MWT) will also be performed. The TUG assess the time taken for the participant to stand up, walk around a cone 3 metres away then return to the seat and sit down. The 6MWT will be a test to see how far the participant can walk within this time frame. In the first sessions, all of these tests may not be achievable due to pain and limited mobility so we will ask participants to do them but they are able to opt out of any tests if they feel they can't complete them.

The time taken to complete the muscle function testing will vary depending on the capability of each individual, however the whole testing battery is not expected to take longer than 45 minutes.

Participants in both groups will be sent away with forms that include a weekly exercise diary, and a diet diary to be completed on 2 days per week. The intervention group will also receive a checklist which needs completing when the supplement is consumed – these only need to be completed for the 4-week intervention period following baseline testing and randomisation.

Nutritional Intervention

The oral nutritional supplement is produced using amino acids, vitamin D and flavourings, the ingredient list can be seen below:

Water, Glucose Liquid, L-Leucine, Sucrose, L-Lysine, L-Valine, Citric Acid, L-Isoleucine, L-Threonine, DLPhenylalanine, L-Hystidine (hcl), DL-Methionine, Cholecalciferol, Potassium Sorbate, Xantham Gum, Orange and Passionfruit Flavourings.

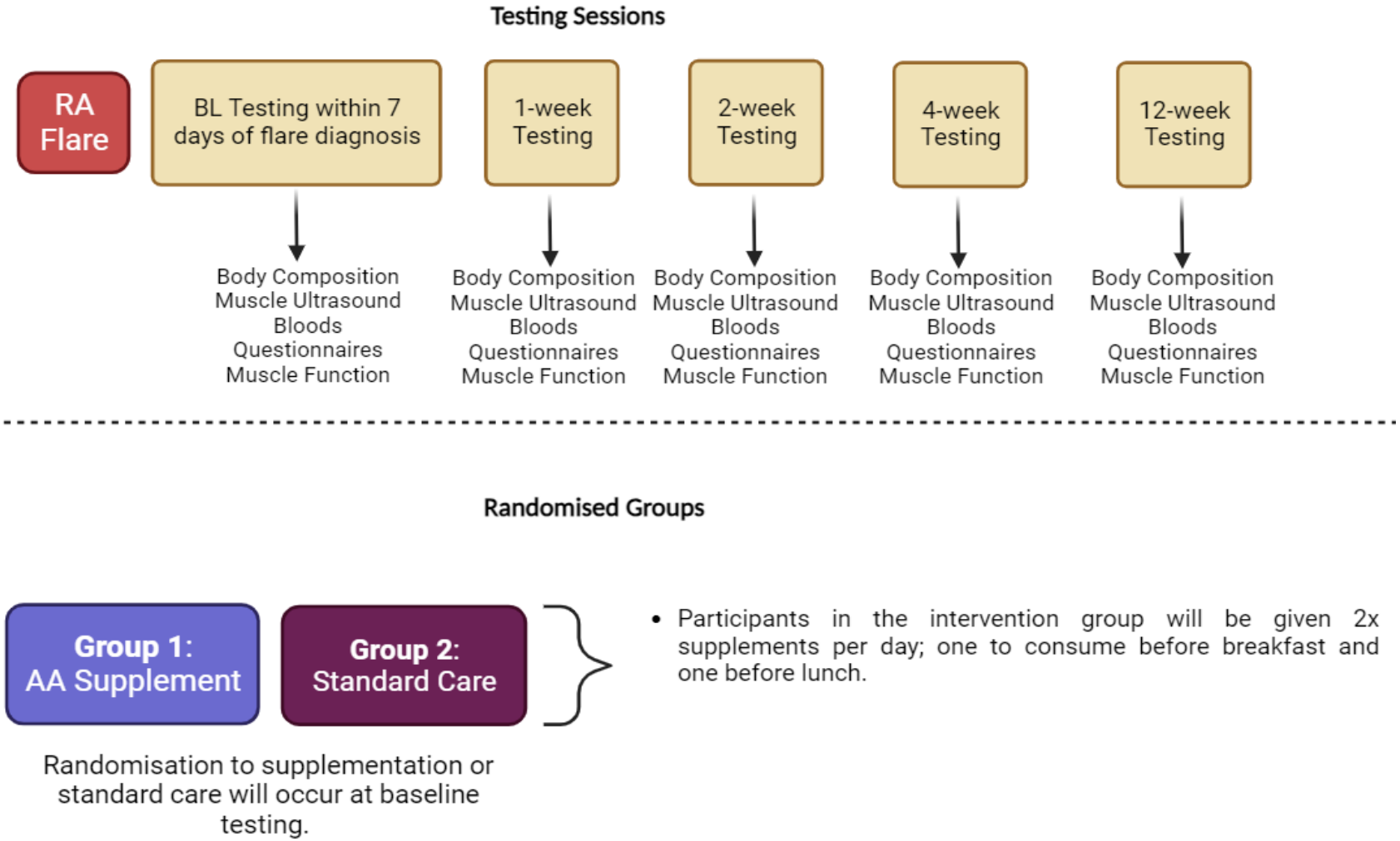
The supplement will be required to be consumed twice per day for 4 weeks. The supplement will be recommended to consume before breakfast and lunchtime meals to supplement amino acid intake at mealtimes. A checklist will be provided to the participants in this group to record their adherence to the supplement. The supplements have been used previously in older adult and clinical populations and have been well received in terms of palatability and no adverse effects have been reported deeming them safe (Older adult populations - Ispoglou et al., 2017; Multiple Sclerosis patient - Ispoglou et al., 2023; Elective and Emergency Colorectal Cancer Patients - Windle et al, https://frailty-sarcopenia.com/posters/P8.5.pdf). The supplements have also been approved for use in two previous IRAS submissions: Project ID 280595 & 222335.

All procedures outlined above will be repeated 1- , 2- , 4- and 12-weeks following baseline assessment. At each follow-up assessment, participants will also be asked about any complications relating to the study or their general health such as inability to consume the supplement, health issues, or changes to treatments etc.

In case of further flares occurring during the follow-up period, participants will be given the option to restart the study as per for the initial flare (i.e., a new baseline following the second flare, followed by 1-, 2-, 4- and 12-weeks retesting). However, if they prefer to avoid the extra testing, they will still be able to follow the original timeline for follow-up testing.

Testing sessions will be identical for participants in the amino acid supplement and standard care groups.

Schematic of visits to the testing venue and each session's testing requirements:



Key: RA – Rheumatoid arthritis; BL – Baseline

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