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Study Protocol and Statistical Analysis Plan

Title: The role of physical activity and diet within Pulmonary Sarcoidosis

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Research Plan and Protocol

Background Rationale

Sarcoidosis is a non-caseating granulomatous disease (Morand et al., 2015), a condition that involves the inflammation of organs and tissues (NHS, 2013). The granulomas form as a result of lymphocytes cells (Loke et al., 2013) clustering together (National institute of Health, 2013a). Up to 90% of sarcoidosis cases are pulmonary, however the condition can affect numerous other locations, such as, the liver and heart and affects the skin in 25% of cases (Saidha et al., 2012). Pulmonary sarcoidosis prevalence is second only to asthma in young adults for respiratory diseases (Morgenthau & Iannuzzi, 2011). Sarcoidosis affects 1 in 10,000 in the UK (NHS, 2013) with limited research into almost every aspect of the disease.

Physical activity has frequently been suggested as beneficial for sarcoidosis patients (NHS, 2015a). This is due to a host of specific and non-specific benefits to those with the condition. This includes the overall improvement to health including decreased levels of non-communicable diseases as well as lower the risk of depression (NHS, 2015b). Although anyone can suffer from depression, sarcoidosis patients have been shown to have increased levels (Hinz et al., 2012). In addition, physical activity helps not only to slow and stop deconditioning; a major issue within sarcoidosis (Fleischer et al., 2014), but also aids the reversal of this process (Strookappe et al., 2015). However, the condition lacks specific guidelines, unlike similar conditions such as COPD and asthma (ACSM, 2014; National Institute of Health and Care Excellence (NICE), 2016). Due to this, sarcoidosis patients are often given advice on exercise and other forms of physical activity such as walking or dancing that are not underpinned by research specific to their condition and as such are potentially dangerous exercise programmes/advice. Holland et al. (2015) states the unique presentation of ILD, including sarcoidosis, requires modifications of exercise prescription for individuals, which was noted as a key issue by Strookappe et al. (2016) in a systematic review of physical activity and training in Sarcoidosis. In addition to this, the effect of pulmonary sarcoidosis on exercise capacity and strength in comparison to a healthy population is limited and needs further research. Reductions to both exercise capacity and muscle strength indicated by lower results than normative values, are known primary symptoms of Sarcoidosis (Spruit, 2005; Hildebrand et al., 2012; Baughman, 2013),

which continue to get progressively worse with the onset of secondary symptoms such as deconditioning (Mitchell et al., 2012; Fleischer et al., 2014). The symptoms of sarcoidosis, in tandem with the varied manifestations (Skin, liver, heart etc. (Saidha et al., 2012)) of the disease alongside pulmonary, make it incredibly hard for accurate, suitable suggestions for physical activity, especially when considering the current lack of literature. This is highlighted by the role of fatigue within sarcoidosis, which is recognised as a major factor within the disease (Baughman, 2013) and therefore needs considering when creating an exercise prescription plan.

Therefore, increased understanding of the effects of pulmonary sarcoidosis is needed as well as comparison to a healthy age matched control population to allow for the data to be compared alongside other intestinal lung diseases (ILD). Further research into this area is vital as exercise training has been shown to be in some cases just as/more effective than medical treatment across a wide range of chronic conditions (Pedersen & Saltin, 2015). Marcellis et al. (2013) argues rehabilitation should be utilised alongside any pharmacological treatment despite the need for future research on potential benefits. Strookappe et al. (2016) also states further random controlled trials are needed but the effects of physical training seem promising from the current limited research.

Despite Sarcoidosis affecting a significant number of people globally, being second only to asthma in young adults for respiratory diseases (Morgenthau & Iannuzzi, 2011), there is a short supply of research into the condition as well as novel treatments to alleviate the primary and secondary symptoms. Therefore therapies (diet and physical activity) are required to help the condition but also prevent further reductions in QOL.

Aim: The primary aim of this study is to ascertain the physical activity patterns and baseline parameters in those with pulmonary sarcoidosis with regards to perceived physical activity and actual physical activity. The secondary aim of the study is to investigate the effect of pulmonary sarcoidosis in relation to muscle strength and exercise capacity against physical activity, lung function and oxygen saturation and how these differ from healthy normative values.

Primary Outcome: Daily physical activity measures against self-reported (IPAQ).

Secondary Outcome: Demographic data and clinical status (age, gender & ethnicity);

Body fat percent, Lung function (forced vital capacity), functional exercise capacity assessed by six-minute walk test, muscle strength by isokinetic dynamometer and hand dynamometer. Patient reported health status and pulmonary complaints objectified in disease-specific quality of life: Sarcoidosis Health Questionnaire and fatigue score (Fatigue Assessment Scale (FAS)).

Participants

Participants with medically diagnosed pulmonary sarcoidosis will be selected. They will be recruited through support groups and online forums from the known sarcoidosis population. A diagnosis of sarcoidosis will be accepted provided the participant has diagnosed pulmonary sarcoidosis ascertained by self-reporting. Patients will be prospectively recruited following new diagnosis of non-cardiac sarcoidosis. (1 in 10,000 have sarcoidosis of which 90% is pulmonary). Due to lack of research into sarcoidosis, there is not enough evidence to permit accurate power calculations, however, based on previous studies and the proportion of diagnosed cases, n=15 participants will be aimed for and act as a pilot for a larger randomised control trial (power 0.80 [80%], significance $P < 0.05$) excluding drop-out.

Inclusion Criteria:

- Patients with known Sarcoidosis according to ATS/ERS/ WASOG criteria statement
- Age: 18-65 years - Both males and females
- Written informed consent is obtained.
- Access to a computer with Internet

Exclusion Criteria:

- Contraindications to (not able to perform) physical tests or exercise testing - e.g. unstable cardiovascular disease, oncological, cardiac, neurological or orthopedic history making them unable to participate screened by a sub-maximal fitness screening form.
- An injury in the past 6 months that inhibits ability to perform exercise testing by a submaximal fitness screening form.
- Patients with a concurrent and predominant diagnosis of another significant respiratory disorder (for example: asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, or lung cancer) by a sub-maximal fitness screening form.

- Pregnancy
- Physical disability (non-ambulatory patient e.g. wheelchair or bed-bound)
- Inability to obtain informed consent
- Cognitive failure making them unable to give consent or understand questionnaires or instruction.

Experiment Design

This is a prospective cross-sectional observational project, with no intervention. Observational exercise testing will include endurance exercise and muscle strength. Patients participating in this study will be treated according to current guidelines (ATS/ERS/ WASOG). As such, diagnostic procedures or treatment will not be postponed or impacted on by participation in this study. All data will be self-reported and self-referred for voluntary participation. Participants will be invited to attend the laboratory for testing on two occasions to measure physical activity, fatigue, aerobic fitness and muscular strength with exercise testing at the Human Performance lab, Kingston University, London to establish the influence on symptoms, physiological and psychological outcomes. Exercise testing will follow standard guidelines (ACSM, 2016). Travel cost reimbursement will be offered to all participants who attend lab visits.

Appropriate health and risk stratification screening will be performed via a sub-maximal exercise screening form (appendix XI) and any participant with an injury in the past 6 months or a known contraindication (ACSM, 2014) to exercise will be excluded from the study. Inclusion criteria are based on having pulmonary sarcoidosis, aged 18 years or above, and participants may have other forms too but must have pulmonary sarcoidosis.

1. During the two laboratory visits to the Human Performance Lab, patients reported response will be objectified by three standardized questionnaires (IPAQ, SHQ and FAS), pulmonary function tests, mass and stature laboratory data will be recorded.
2. The patient is asked to keep a daily record physical activity by wearing a triaxial accelerometer on their hip to measure daily physical activities and ambulatory movements for 7 days.

Lab Procedures

During visit one, participants will sign informed consent forms (appendix II) and have any questions answered before continuing. They will then be put through a screening process beginning with physical examination: characteristics such as anthropometric data (stature, mass, heart rate (HR), blood pressure, age, BMI, fat% (Bodpod, Cosmed/ Bioelectric Impedance Analysis (BIA), Tanita) will be collected. Following this, participants will conduct a lung function test via computer spirometry (Oxycon Pro, VIASYS GmbH, Eric Jaeger, Hoechst, Germany), their predicted results will be corrected for ethnicity (Bellamy, 2005) allowing an accurate percentage of lung function to be recorded. Caucasian results remain the same, whilst Black-Caribbean are decreased by 13% (Bellamy, 2005). Participants will then conduct muscle strength testing of key muscle groups using an isokinetic dynamometer (Biodex System 4, Biodex Corporation, NY, USA); tests include: elbow flexor muscle strength (EFMS), quadriceps peak torque (QPT) and hamstring peak torque (HPT). In addition to this handgrip strength will also be assessed via handgrip digital dynamometer (Accord Medical Products). A minimum rest period of 20 minutes will follow (Vainshelboim et al., 2014) based on exercise-based pulmonary rehabilitation research. Heart rate (bpm) will be checked at the end of this period and in two minute intervals until HR returns to baseline as per ACSM (2014) guidelines. Physical testing will not take place until this return to baseline. Following this rest period participants will conduct a six-minute walk test (6MWT) during the test participants will be measured for Borg rate of perceived exertion and Borg Dyspnoea at 2 minute intervals and at completion of the test and oxygen saturation levels of participants will be recorded during the 6MWT via a portable pulse oximeter. Once the 6MWT has been completed participants will complete three questionnaires, the fatigue assessment scale (FAS; De Vries et al., 2004), international physical activity questionnaire (IPAQ; Ekelund et al., 2003) and Sarcoidosis Health Questionnaire (SHQ; Cox et al., 2003). Before leaving, participants will be given tri-axial accelerometers (GT3X+ accelerometer, Actigraph), which will be used to measure the participants physical activity (PA) for seven days, to establish habitual physical activity levels and compare against the results of the IPAQ.

During the second lab visit, participants will return their accelerometers and follow the same pattern of testing from the first visit, excluding the questionnaires (SHQ, FAS & IPAQ) and anthropometric information. The order of testing will follow ACSM (2016)

guidelines therefore strength and aerobic/anaerobic capacity will be first. Alongside this, age-matched healthy participants with no known interstitial lung disease (ILD) or other condition linked to reduced physical activity will used as a comparison between sarcoidosis and healthy populations.

Statistical analysis

A mixed model repeated measures analysis of variance (ANOVA) will be utilized, in addition to correlations and regressions.