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The Effects of Physical Activity on Disease Activity in Patients with Rheumatoid Arthritis

By

Alessandra Prioreschi

A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of

Doctor of Philosophy

University of the Witwatersrand

2014

Declaration

I declare that this thesis entitled 'The Effects of Physical Activity on Disease Activity in Patients with Rheumatoid Arthritis', submitted for the degree of Doctor of Philosophy is the result of my own work and that where reference is made to the work of others, due acknowledgement is given.

I also certify that any material in the thesis has not been submitted for degree or for examination purposes to any other university of institution.

Alessandra Prioreschi

Signed…….

October 2014

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Operational Definition of Terms

Activity counts: Units of measurement of physical activity produced by the Actical accelerometer. Counts provide a quantitative measure of activity intensity and allow for classification of activity levels as well as monitoring of changes in activity levels. Activity counts are generated from the acceleration signals detected by the device, which are then amplified, filtered, digitized, and full wave rectified in order to be converted into activity counts (1).

Black: Throughout this dissertation the term 'Black' has been capitalised as suggested by Bhopal in 2004 (2). The most widely used human racial[1] categories are based on visible traits (especially skin colour, facial features and hair texture), genes, and self-identification (3).

Light, moderate and vigorous activities: These are all activities that increase energy expenditure above resting levels and are classified into specific thresholds as calculated by the Actical software using the activity counts generated per minute epoch. Thus; light activity is defined as activity that generates counts between 100 and 1535 (i.e.: 1.5-2.9 metabolic equivalent units (METs), where one MET is the energy cost of resting quietly and is defined in terms of an oxygen uptake of $3.5mL.kg^{-1}.min^{-1}$ (4)); moderate activity generates counts between 1535 and 3962 (3-6 METs), and vigorous activity generates counts above 3962 (>6 METs).

Physical activity: This refers to habitual activities that raise energy expenditure levels above that of resting, and can include leisure activities, ambulatory activity or conscious exercising. However, in the case of the patients with RA used in this study, it refers mostly to ambulatory, habitual activities.

[1] The word 'race' does not refer to any biological attributes but rather to the compulsory classification of people into the Population Registration Act. Although the act has been repealed, these categories are still powerful and commonly used by South African government and statistical services.

Sedentary activity: This is any activity falling into the sedentary threshold as calculated by the Actical software using the activity counts generated per minute, and generally comprises of activities that do not increases energy expenditure above that of resting (such as sitting or lying down). Typically, this includes activities in which activity counts generated are less than or equal to 100 (i.e.: 1-1.5 METs).

Abbreviations

BMD: Bone mineral density

BMI: Body mass index

CRP: C-reactive protein

CDAI: Clinical disease activity index

DMARD: Disease modifying anti-rheumatic drug

DXA: Dual X-ray absorptiometry

HAQ: Health Assessment questionnaire

HRQoL: Health-related quality of life

MDGA: Physician global assessment of disease activity

PGA: Patient global self-assessment of disease activity

PPA: Patient pain assessment

RA: Rheumatoid arthritis

SDAI: Simplified disease activity index

SF-36: Short form-36 questionnaire

SJC: Swollen joint count

TJC: Tender joint count

T score: A standardised measure of bone health comparing an individual's BMD to that of a healthy, sex matched reference value of peak bone mass

WBV: Whole body vibration

WHO: World health organisation

Z score: A standardised measure of bone health comparing an individual's BMD to that of a healthy, age, sex and ethnicity matched reference value

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Most importantly, thank you to the ladies who took part in my research and gave so willingly of their time. I will remember every single one of you and the times we shared together, and have learnt so much from you and your experiences.

Publications and Presentations

The work presented in this thesis is based on the following publications and presentations that have emanated from my research[1].

Peer Reviewed Publications:

1. **Prioreschi A, Hodkinson B, Avidon I, Tikly M, McVeigh JA**. The clinical utility of accelerometry in patients with rheumatoid arthritis. Rheumatology. 2013:52(9):1721-1727. DOI:10.1093/rheumatology/ket216.
2. **Prioreschi A, Hodkinson B, Avidon I, Tikly M, McVeigh JA.** Changes in Physical activity measured by accelerometry following initiation of DMARD therapy in patients with rheumatoid arthritis. Rheumatology. 2014:53(5);923-6. DOI:10.1093/rheumatology/ket457.
3. **Prioreschi A, Tikly M, McVeigh JA**. A three month controlled intervention of intermittent whole body vibration designed to improve functional ability and attenuate bone loss in patients with rheumatoid arthritis. Under review at BMC Musculoskeletal Disorders.
4. **Prioreschi A, Makda M, Tikly M, McVeigh JA**. Higher habitual activity levels are protective of bone mass in patients with rheumatoid arthritis. Under review at BMC Musculoskeletal Disorders.
5. **Prioreschi A, Makda M, Tikly M, McVeigh JA.** Positive effects of a 12 week WBV intervention on functional ability, bone mineral density and fatigue are sustained in a population with RA. Submitted to International Journal of Bone and Mineral Research.

[1] For each of the abovementioned publications, I was responsible for conceptualisation of the study, data collection, and statistical analysis, interpretation of the data, and drafting and editing of the manuscript. Please refer to Appendix 14 for more details regarding author contributions.

Conference Presentations:

1. 22nd Biennial South African Rheumatism and Arthritis Association National Congress, Muldersdrift, South Africa, September 2011: Oral Presentation.
2. 17th European College of Sports Science Congress, Bruges, Belgium, July 2012: Poster Presentation.
3. University of the Witwatersrand and Faculty of Health Science Biennial Research Day and Postgraduate Expo, Johannesburg, South Africa, September 2012: Poster Presentation.
4. 4th Cross Faculty Research Symposium, University of the Witwatersrand, Johannesburg, South Africa, October 2012: Poster Presentation.
5. 23rd Biennial South African rheumatism association and 7th African League Against rheumatism congress, Durban 2013: Oral Presentation.
6. Annual European Congress of Rheumatology, Madrid, Spain 2013: Oral Presentation.
7. 18th Annual Congress of the European College of Sports Science, Barcelona, Spain 2013: Oral Presentation.
8. 5th Cross Faculty Symposium, University of the Witwatersrand, Johannesburg, South Africa 2013: Oral Presentation

Honours, Grants and Awards:

1. 1st place winner for the best oral presentation at the 22nd Biennial South African Rheumatism and Arthritis Association National Congress, Muldersdrift, South Africa, September 2011.
2. European College of Sports Sciences Young Investigators Award Travel Grant, 2012 and 2013.
3. 1st place winner for the best student poster presentation at the University of the Witwatersrand Faculty of Health Science Research day.

Preface

Don't wish it were easier, wish you were better. Don't wish for fewer problems, wish for more skills. Don't wish for less challenges, wish for more wisdom.

- Earl Shoaf

When I started this journey I had very little understanding of what a diagnosis of rheumatoid arthritis actually meant. I was aware of the fact that patients with rheumatoid arthritis suffer from chronic pain and inflammation, and that they are therefore unable to function normally – the classic prelude to most research articles discussing rheumatoid arthritis. What I did not understand is what this means for the patient in reality. What does 'chronic pain' mean? What does the 'inability to function normally' mean? These terms are used so often that they almost become meaningless. It is difficult to understand or to explain what these terms mean for the patients who suffer them, but through my years of working with patients with rheumatoid arthritis on a very personal and involved basis, I started to get some idea. To not be able to get out of bed in the morning, to be unable to take a bath without assistance, to be unable to pick up your crying grandchild – these unthinkable situations are merely daily truths in the lives of patients suffering with rheumatoid arthritis. Without dramatising the stark reality of these lifestyles, I would just like to draw attention to the strength that these patients have. The ladies I worked with throughout my research greeted me everyday with a smile, through the cold winter months when their pain was "unbearable", and truly taught me a lesson in appreciation of being healthy. I am so grateful for this experience. It is so easy, whilst pursuing a degree such as a PhD, to get caught up in the academia and necessity to publish your work and analyse your data, that one can often forget why the research is being conducted in the first place. I hope that what I have presented in the next few pages can be of some benefit to patients living with rheumatoid arthritis. It is so important that we as researchers, clinicians, specialists, or allied medical professionals, do whatever we can to enlighten each other with the knowledge we pursue and skills we develop. In doing so, we can work together to provide the best care to our patients and hopefully make their lives a little bit easier.

Abstract

Rheumatoid arthritis (RA) is an autoimmune condition with a predilection for peripheral synovial joints. It affects 0.5 to 5% of the adult population worldwide. The chronic inflammation of RA results in destruction of the synovial joints, decreased mobility and chronic pain. Patients who have RA experience a poorer health related quality of life (HRQoL) in comparison to the general population. They are less habitually physically active than a healthy population, to the point of not meeting the required guidelines of physical activity to maintain a healthy wellbeing. Moreover, patients with RA are prone to developing osteoporosis as a consequence of systemic inflammation and a sedentary lifestyle.

The aims of the research undertaken for this thesis were to: 1) objectively quantify habitual physical activity levels in RA patients in comparison to a healthy population, 2) ascertain any associations between habitual activity levels and disease activity in patients with RA, 3) determine the changes in habitual physical activity levels in patients newly diagnosed with RA in response to commencement of DMARD therapy, 4) determine the predictive factors causing the changes seen in disease activity in response to commencement of DMARD therapy in patients with RA, 5) determine the associations between habitual physical activity levels and bone health in patients with RA, and 6) determine the effects of a WBV therapy intervention on functional ability, and bone health, as well as on disease activity and habitual physical activity levels in patients with RA. These aims were addressed by conducting three studies.

In the first study habitual physical activity levels was assessed over a two week period in a cohort of 50 female RA patients in comparison to 22 healthy matched control participants, using an Actical accelerometer. Patients also completed various disease activity questionnaires, namely the Health assessment questionnaire (HAQ), and the Short Form-36 questionnaire (SF-36), and were assessed for rheumatoid disease activity by a physician using the simplified disease activity index (SDAI). All data are presented as mean (SD). The RA patients had a disease duration of 99(77) months, with moderate functional disability (HAQ score of 1.3(0.9)) and moderate disease activity (SDAI score of 18.38(11.76)). Patients had a poor HRQoL as assessed by the SF-36 with a score of 44(18). Accelerometry showed that the RA group spent significantly more time in sedentary behaviours than did the control group, spending 71(11)% of their awake day in sedentary activities as opposed to 62(11)% in the control group ($p<0.01$). The RA group had significantly lower mean activity counts in the morning ($p<0.01$) and the late afternoon ($p<0.01$) than the control group. Within the RA group, patients who were more physically active scored significantly better in many components of the SF-36, indicating an association between better HRQoL and increased habitual physical activity levels. The HAQ scores, corrected for age and disease duration, correlated negatively with physical activity levels in the RA group ($r^2=0.12$, $p=0.03$).

In the second study habitual physical activity levels were observed longitudinally in 18 RA patients before and three months after commencing DMARD therapy. The accelerometer was worn for two consecutive weeks before and after starting DMARD therapy. Patients also completed the same disease activity assessments as the patients in Study 1. The RA group was compared to a matched control group of 18 healthy participants. After three months of DMARD therapy, RA patients improved

significantly on all measured indices of disease activity and accelerometry metrics. The activity counts in sedentary activities declined from a mean (SD) of 995(283) to 837(253) counts, $p<0.01$, whilst light activities increased from a mean (SD) of 3461(1453) to 4451(92057) counts, $p=0.04$, indicating increased habitual physical activity levels after commencing DMARD therapy. Moreover, significant differences in mean activity counts observed between the control and RA groups in the morning ($p=0.05$) and afternoon ($p=0.02$) at baseline, were attenuated after three months of drug therapy, to the point where habitual physical activity levels were equivalent between the groups throughout the day. Multiple regression analysis showed that change in early morning stiffness was most strongly predicted by change in sedentary and moderate activity ($\beta=0.69$, $p=0.04$ and $\beta=-0.93$, $p=0.02$ respectively), while a fall in CRP levels was most strongly associated with change in moderate activity ($\beta=-0.92$, $p=0.03$). Spearman's correlation tests showed further positive associations between improvements in physical activity and improvements in disease activity.

In the third study, the effects of 12 weeks of whole body vibration (WBV) therapy in stable and established RA was studied by randomising patients to either a WBV therapy group (n=16) or a standard care control group (CON, n=15). All data are presented as mean (SD) or mean (SEM). Patients were fitted with an accelerometer for a one week period, completed the same questionnaires as done in the previous two studies, and had dual X-Ray absorptiometry (DXA) scans to measure BMD and body composition at baseline, end of therapy and 12 weeks post-therapy.

Patients in the WBV and CON groups were well matched at baseline for all variables. During baseline analysis, all patients were divided into two subgroups – those with normal bone mass (n=21), and those with low bone mass (n=8). Compared to

subgroup of patients with low bone mass (n=8), the subgroup of patients with normal bone mass (n=21) reported less functional disability (HAQ score (0.96(0.71) vs. 1.57(0.74), p=0.05) and had a trend towards lower RA disease activity as assessed by CDAI (7.7(6.1) vs. 13.8(10.8), p=0.07). The normal bone mass subgroup also had higher overall habitual physical activity (p<0.01). They spent on average two hours less per day in sedentary activity (65(4) vs. 73(2) % time per day, p<0.01), over 70 minutes more time in light activity (23(1) vs. 18(2) % time per day, p<0.01), and over 50 minutes more in moderate activity per day (12(3) vs. 8(2) % time per day, p<0.01), than the low bone mass subgroup. The normal bone mass subgroup broke up their sedentary time more frequently per day than low bone mass subgroup (72(21) vs. 53(18) times per day, p=0.03). Patients who met the minimum recommended physical activity guidelines for a rheumatic population had significantly better Z scores at the hip than those who failed to meet the minimum guidelines (p=0.03).

Thereafter, at the end of the 12 week intervention, the patients who underwent WBV therapy experienced significant improvements in HAQ scores (1.22(0.19) to 0.92(0.19), p=0.02), fatigue levels assessed by a self-report Lickert scale (4.4(0.63) to 1.1(0.65), p<0.01), and whole body BMD (1.09(0.03) to 1.10 (0.03) $g.cm^{-2}$, p=0.05). By contrast, in the CON group there was no significant change in HAQ scores or fatigue levels, and whole body BMD declined significantly (1.07(0.03) to 1.05(0.03) $g.cm^{-2}$, p<0.01), while a significant increase was seen in the WBV group (1.09(0.03) to 1.10(0.03) $g.cm^{-2}$). Rheumatoid disease activity remained stable in both groups throughout the intervention period. Ten minute bouts of light and moderate physical activity were significantly reduced in the CON group over the intervention period (2.8(0.61) to 1.8(0,64) bouts/day, p=0.01), but were preserved in the WBV group (3.1(0.59) to 3.0(0.61) bouts/day, p=0.70). Twelve weeks post therapy, fat mass was

decreased (37(3) to 35(3) kg) in the WBV but increased in the CON group (31(3) to 35(3) kg, $p<0.01$), while lean mass decreased in the CON group (42(2) to 40(2) kg), and was increased in the WBV group (46(2) to 45(2) kg, $p<0.01$). In summary this study showed that intermittent WBV results in sustained improvements in functional ability, attenuation of bone mass loss at the hip, and improvement in fatigue levels in established RA.

Altogether, these studies demonstrate that RA patients are indeed more sedentary in comparison to a healthy, matched control group, and that habitual physical activity levels measured by accelerometry correlate with patient-reported functional ability. Accelerometry measures were found to be responsive to change in relation to disease activity. Besides improving RA disease activity indices, DMARD therapy increased habitual physical activity levels and patterns of daily physical activity in RA patients started to resemble those of the control group. The research also showed that BMD is positively associated with increased habitual physical activity in RA patients and, lastly that WBV therapy improved functional ability and fatigue levels, and attenuated bone loss at the hip, without significant impact on rheumatoid disease. Hence, increased habitual activity needs to be encouraged, and WBV therapy is a feasible, safe and simple intervention for improving functional ability, HRQoL, and BMD in patients with established RA.

Chapter 1: Literature Review

1.1. Introduction:

This chapter will examine rheumatoid arthritis (RA) as a disease, bone health in RA, medical treatments for the disease, and traditional outcome measures used in RA. The use of accelerometry as an objective measure of physical activity will be reviewed. Exercise interventions for the treatment of RA will be explored, including the role of whole body vibration (WBV) therapy in chronic musculoskeletal diseases. This chapter will conclude with an introduction to the problem that this thesis aimed to address.

1.2. Rheumatoid Arthritis:

Rheumatoid arthritis (RA) is an autoimmune condition with a predilection for peripheral synovial joints. The disease affects 0,5 to 5% of the adult population worldwide, with the prevalence being at least two times higher in women than in men (5). RA is the most common immune-mediated inflammatory arthritis (6-7).

Immunologically, the destruction of joints and swelling resulting from RA is due to the synovial inflammation and proliferation, known as pannus, which histologically shows infiltration of $CD4^+$ T cells, B cells, and macrophages which organise into lymphoid aggregations with germinal centres (6). Local proteolytic enzymes are induced that degrade surrounding cartilage and subchondral bone. Pannus produces many pro-inflammatory interleukins (IL), such as IL-6, IL-1, IL-15, IL-18, tumour necrosis factor alpha (TNF-α), and an array of chemokines (6).

The exact aetiology of RA is largely unknown (7), but there is evidence that

hereditary factors and environmental factors such as smoking, and certain infectious agents predispose to the disease (8). Rheumatoid arthritis is also strongly associated with class II human leukocyte antigens, HLA-DR4 and DR1, indicating a genetic association (6). However, like all autoimmune conditions, a combination of events needs to take place for the disease to develop, namely: having a genetic background, the activation of the innate immune system due to an unknown environmental trigger, and the adaptive immune responses that ensue. Several genes have been shown to play a part in susceptibility to RA, yet twin studies have shown that genes are responsible for only 50% of the risk for RA; with the other 50% being attributed to environmental factors, as well as stochastic, or chance factors (8). Infectious agents such as Epstein-Barr Virus (EBV), mycobacteria and parvoviruses have been known to trigger RA in genetically predisposed individuals (9). Eighty percent of patients with RA have antibodies directed against EBV, and RA perpetuates the response against EBV (10)

The cardinal clinical features of RA are prolonged early morning stiffness of the joints, lasting for more than 30 minutes (11), and swelling and tenderness of the small joints of the hands and feet (pain in these areas is usually among the first noticeable symptoms) (6). The chronic inflammation of RA results in destruction of the synovial joints, decreased mobility and chronic pain (12). The presence of constant pain limits the ability of patients with RA to function normally, and as a result, physical activity levels are lowered. Rheumatoid arthritis is thus characterised by synovial swelling and inflammation, autoantibody production, and deformity due to cartilage and bone destruction. Systemic inflammation further results in comorbidities affecting the heart, lungs, bone, central nervous system, and host immunity to infections and cancers (13).

Diagnosis of RA is not always easy, and hence classification criteria for RA have been developed mainly for research purposes but also as guide to the practicing clinician. These classification criteria have undergone a number of revisions. The 1987 American College of Rheumatology (ACR) criteria being applied in this work are shown below in Table 1.1 modified from Braun & Sieper, 2009 (11), yet more recent 2010 ACR/European League Against Rheumatism (EULAR) revised criteria have been developed in order to increase detection of early disease[2].

Table 1.1 The 1987 ACR classification criteria for rheumatoid arthritis

1	Morning stiffness in and around joints lasting at least 1 hour before maximal improvement
2	Soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician
3	Swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints
4	Symmetric swelling (arthritis)
5	Rheumatoid nodules
6	The presence of rheumatoid factor
7	Radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints
	Criteria 1 to 4 must have been present for at least 6 weeks. RA is defined by the presence of 4 or more criteria, and no further qualifications (classic, definite, or probable) or list of exclusions are required.

[2] The ACR together with EULAR have developed the new 2010 RA classification criteria (176). These criteria were developed specifically to facilitate the classification of RA patients with early disease, rather than to diagnose established RA disease. These criteria are therefore more sensitive and are aimed at preventing patients from reaching a chronic, erosive disease state (as defined by the 1987 criteria). The 2010 criteria assess level of joint involvement, serology, acute-phase reactants, and duration of symptoms.

Diagnosis of RA is made on the basis of phenotypic features rather than the underlying pathogenic mechanisms causing these features (14).

Laboratory features of RA include inflammatory markers such as elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in active disease, and autoantibodies such as rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPAs) (9). Rheumatoid factor is an antibody directed at the fragment crystallisable (Fc) region of immunoglobulin G (IgG), (typically involved in the secondary immune response). It was first discovered by Waaler in 1939, and only later further characterized as an antibody by Kunkel in 1957 (15). The discovery and classification of RF was the first evidence classifying RA as an autoimmune condition. Eighty percent of RA patients are RF positive, and the presence of RF normally indicates more severe disease progression (6), yet RF is also seen in other inflammatory diseases and sometimes in healthy individuals (9). The more recent discovery of ACPAs, which are thought be more specific than RF, are also found in about 80% of cases (16).

Rheumatoid inflammation can result in extra articular manifestations affecting organs such as the eyes (sicca syndrome, scleritis), lungs, heart, brain, and skin (vasculitis) (8). In addition, a multitude of comorbidities have been associated with RA as a result of the chronic inflammatory process inherent to the disease. The increased mortality in patients with RA is largely attributed to cardiovascular events. Of these, ischemic heart disease is the most common, including heart attacks and sudden cardiac death (8). Cardiovascular disease present in patients with RA is often not explained solely by the traditional risk factors, but also by the chronic inflammatory process (13). Patients with RA are also at increased risk of developing osteoporosis, infections such

as tuberculosis, and non-Hodgkins lymphoma (13). Metabolic syndrome, fatigue, and depression also frequently occur. Furthermore, the musculoskeletal system is most severely affected, as will be explored in subsequent sections.

1.3. Outcome Measures in Rheumatoid Arthritis:

1.3.1 Disease Activity:

Measuring disease activity is important for several reasons: 1) measuring disease activity helps the clinician to adjust medical therapy and 'treat-to-target', 2) ongoing poorly controlled disease activity is associated not only more with permanent physical disability, but also with increased risk of premature death, and 3) ongoing disease activity increases the risk of extra articular diseases such as rheumatoid vasculitis (17).

There are many individual measures of disease activity in RA, such as the acute phase reactants (CRP), pain, and joint swelling; yet no single clinical parameter measures the total burden of inflammation in RA. Over the last 20 years, EULAR, along with the WHO and the International League Against Rheumatism (ILAR), have therefore developed a core set of variables that should be assessed, namely: swollen joint counts (SJC) and tender joint counts (TJC), both of which are calculated by palpation of 28 upper and lower limb joints; patient global self assessment (PGA); physician global assessment of patient (MDGA); patient pain assessment (PPA) and the concentration of an acute phase reactant (18). Composite scores have been developed to assist with consistency of diagnosis and to guide therapy decisions, improve patients understanding of their disease, and to attempt to improve outcomes through the use of a more consistent evaluation, specifically for use in clinical trials. The original composite score used was the 44 Joint Disease Activity Score (DAS-44), followed by the 28 Joint Disease Activity Score (DAS-28), and more recently the Simplified

Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI), which are essentially based on the DAS-28. Three such composite measures have been validated for South African populations: the CDAI, the SDAI, and the DAS-28 (19). The SDAI and CDAI were used in this research and are calculated as shown below in Equation 1 and Equation 2 respectively:

SDAI=TJC+SJC+MDGA+PGA+(CRP/10)

……Equation 1.

CDAI=TJC+SJC+MDGA+PGA

……Equation 2.

These simple numerical calculations allow for a quick and easy assessment of disease activity, far simpler than the calculation of the DAS-28. Furthermore, the inclusion of the physician global assessment in the CDAI and SDAI makes these scores somewhat more objective than the DAS-28 (which only includes the patient global assessment). CDAI is even simpler and quicker to calculate due to the lack of an acute phase reactant such as CRP, which requires analysis of blood results that take time, and are often missing from patient files leading to inconsistency. However, the inclusion of CRP in SDAI does confer some benefit in terms of validity as an outcome measure, as it has been shown to be the most reliable acute phase reactant, and is responsive to change in disease activity (18)). Both CDAI and SDAI are well validated, and have been shown to correlate very well with each other, as well as with the DAS-28 (18). The calculation of these scores also allows for patients with RA to be categorized according to severity of disease activity using the following cut offs:

Table 1.2. Cut-offs for rheumatoid disease activity and outcome assessments

HAQ Score		SDAI Score		CDAI Score		SF-36 Score	
Low impairment	<0.75	Remission	<3.3	Remission	<2.8	Poor outcome	<66
Moderate impairment	<1.75	Low disease activity	<11	Low disease activity	<10	Good outcome	>66
High impairment	>1.75	Moderate disease activity	<26	Moderate disease activity	<22		
		High disease activity	>26	High disease activity	>22		

This scoring system allows for comparisons to be made between RA patients, as well as for the individual RA patient before and after therapy; and the quantifiable score makes for an easier understanding of disease activity. Scoring also allows for decisions to be made with regards to drug therapy, as well as allowing for a 'treat to target approach', such as treating to achieve low disease activity or remission (as discussed further in Section 1.4.).

Rheumatoid arthritis has a disease progression typical of an autoimmune disease that consists of day to day fluctuations in symptoms, as well as flare ups and periods of remission. It is important to measure the status of the joints by assessing inflammation, structural damage and general physical status (20). Direct palpation of the joints is the easiest measure of joint inflammation, yet is unquantifiable. Magnetic resonance imaging and ultrasound provide a more quantifiable measure of joint status, yet are not always available and are expensive (20). These measures are therefore not used routinely in clinical trials or in clinical practice. Composite measures of disease activity give a better idea of overall disease status.

1.3.2 Functional Disability and Health Related Quality of Life:

Patients with RA have long been shown to have a decreased health related quality of life (HRQoL) compared to the general population (21). This is largely due to the presence of chronic pain and joint deformities. Health related quality of life, defined as the physical, emotional and social aspects of life which are affected by a patient's disease or their treatment, is a relevant measure of disease activity according to the WHO (22), and studies have shown that "feeling well" is an important patient outcome, along with the management of pain, sleep, fatigue, emotional- and physical wellbeing (21). Short term outcomes such as pain and fatigue are becoming more important to treat, as well as to understand, due to the importance of "feeling well". Fatigue in RA is caused by to the systemic effects of inflammation on the brain and disturbed sleep patterns, and is measured as an outcome of RA disease activity (8). The ability to positively affect fatigue levels is one of the most prominent benefits of current cytokine antagonist drugs (8).

Decreased functionality is another important aspect of RA, and once again, functional ability is used to measure treatment effects in RA as a means to assess how patients feel and function in normal daily life (8). Pain has been correlated with decreased physical activity in other chronic diseases, such as fibromyalgia (23) and osteoarthritis (24). Furthermore, habitual participation in vigorous activities has been shown to decrease pain sensitivity in healthy females (25). In RA, swollen and tender joints force patients into a sedentary lifestyle (22). This decrease in physical activity is worsened by the joint and muscle damage occurring during severe disease, which results in disability and muscular atrophy (25), further decreasing physical activity (Figure 1.1). Some patients with RA lose their ability to work due to their disease,

resulting in an economic burden on society, as well as increasing the patient's financial stress, a common problem in developing countries such as South Africa (26).

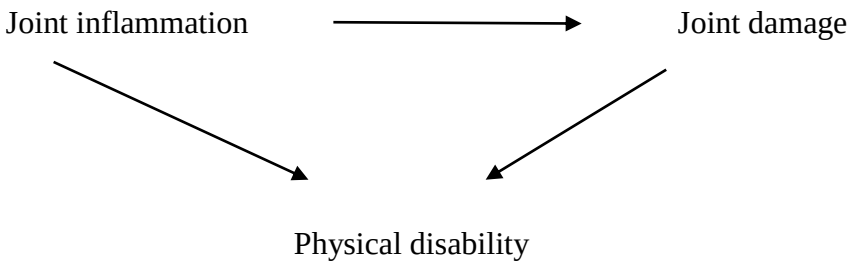


Figure 1.1. Relationship between joint inflammation, damage, and disability in RA

The concurrent effects of persistent pain and decreased physical activity and functional ability lead to disturbances in sleep patterns, which worsens daily functioning and further perpetuates pain. Pain is the leading cause of insomnia, yet at the same time, sleep can alter pain thresholds (27). The disease process of RA, as well as the medication taken for it, disturbs sleep patterns in more than half of RA patients, which can lead to increased stiffness, and hence pain the next day (27). Increased pain leads to a decreased ability to be active and therefore decreased physical activity (23), which in turn contributes to disturbed sleep patterns (27).

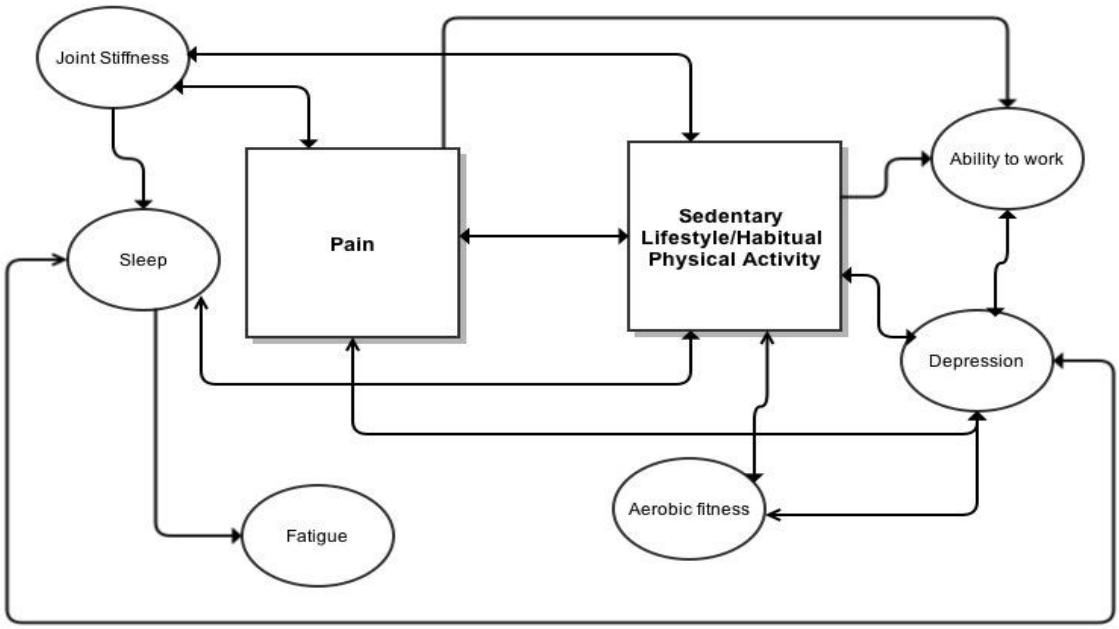


Figure 1.2. Relationship between factors that affect health related quality of life in rheumatoid arthritis on pain and habitual physical activity levels.

In addition, patients living with a chronic pain condition such as RA have been shown to have a 13 to 20% prevalence of depression, which is two to three times greater than the prevalence in the general population (22). Depression has been associated with decreased functionality and physical activity (22). There is a strong association between sleep, pain, depression and decreased physical activity and functionality, and it is probable that these factors have a bidirectional causal relationship with each other and RA disease activity (Figure 1.2), and all of these factors should be considered when treating patients with RA.

There has therefore been a shift towards measuring outcomes that are important to patients with chronic diseases, and specifically with RA. The Health Assessment Questionnaire (HAQ) was developed originally by Jim Fries at Stanford when his group popularised the concept of the 5 Ds of RA, i.e.: death, discomfort, disability, drug (therapeutic) toxicity, and dollar cost (28). The modified, shortened version of this questionnaire, the mHAQ (referred to from here on as the 'HAQ') is most commonly used and is as sensitive as the original version, and comprises of three out of the six ACR outcome measures (29). The questionnaire is self-administered and takes approximately five minutes to complete and one minute to score. It assesses fine movements of the upper and lower extremities, as well as locomotor movement of both the upper and lower limbs. The questionnaire is comprised of 20 items assessed in eight domains, namely: rising, dressing, walking, hygiene, eating, reach, grip, and usual activities. Patients score each item in terms of difficulty on a scale of 0-3 (0=no difficulty, 1=some difficulty, 2=much difficulty, 3=unable to do) and a total score is then calculated (the outcome of which is assessed using the cut-offs shown in Table 1.2). The HAQ is a well validated assessment of functional capacity in patients with

RA (29), and accurately reflects joint inflammation and disease activity (19). The HAQ has been validated in Black RA populations in South Africa (30), and is therefore recommended for the assessment of disability in South Africa (19).

While the HAQ can predict both long- and short-term outcome with regards to disease progression of RA (31), it is still important to measure HRQoL as a measure of the success of treatments for these patients. The Short Form-36 (SF-36) is a general health status questionnaire which describes the impact of disease on patient outcomes, and has been well validated for use in patients with RA, correlating well with HAQ scores (31). While HAQ is specific to RA disease, SF-36 can compare HRQoL across various diseases. The SF-36 consists of questions in eight domains of health, namely: physical function, role physical, body pain, general health, vitality, social functioning, role emotional, mental health and reported health; all of which are separated into either composite physical health or composite mental health scores, and combined to give a total SF-36 score from 0-100, where a higher score indicates a better outcome (as shown in Table 1.2). The SF-36 has been successfully used for assessment of HRQoL in Black, South Africans with RA (32). Outcome factors such as pain and fatigue are often measured independently using self-reported measures such as Lickert scales, due to their importance in patient perceived well being (8).

Although functional ability has been shown to be one of the most important outcomes for patients with RA, as well as the most commonly assessed RA outcome (33-34), the current methods of assessing functional ability (HAQ, and certain domains of the SF-36 questionnaire) are subjective, and no routine objective assessment of physical functional ability exists for patients with RA. In fact, objective physical activity levels are not routinely measured in RA patients in clinical practice.

1.3.3 Damage (Irreversible)

Joint destruction and bone erosion are also routinely measured in clinical practice, using radiographs, as well as quantitative assessments of bone damage such as X-Rays (8), and scores such as the rheumatoid arthritis articular damage score (RAAD) (35), and the Sharp scoring method (36). Eroded bone and articular damage in RA is largely irreversible (8), and while it is important to measure the extent of this damage; it is imperative to measure and understand reversible disease activity factors such as those mentioned above, as a means to monitor response to therapy and treatments.

1.4. Principles of Management of Rheumatoid Arthritis:

1.4.1 Medical Treatment:

Since there is no definite cure for RA, treatments aim to decrease the symptoms of pain and disability. Physical disability negatively affects social lives, employment and personal care (19). Drugs used in the treatment of RA are designed to limit pain and decrease inflammation (thereby limiting damage), and should therefore improve ability to function normally in daily life. South African recommendations for management of RA, like those of EULAR and ACR, recommend that drug treatment regimes should be designed to achieve low disease activity or remission (See Section 1.3). Decreasing disease activity allows for better physical function, as well as decreased structural damage (19).

The most widely prescribed class of drugs used to treat RA are synthetic or traditional disease modifying antirheumatic drugs (DMARDs). These drugs inhibit or halt the process of RA disease progression (37). The most commonly prescribed drug within this class of drugs is methotrexate (19, 38) Methotrexate has an excellent safety profile, and is either used as monotherapy, or as combination therapy with other

DMARDs depending on disease severity (19). Other drugs used for symptomatic treatment of RA include non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics that are used to decrease the pain and stiffness experienced, and are usually prescribed 'as needed'. Glucocorticoids such as prednisone are used to treat inflammation, either orally in conjunction with DMARDs, or injected locally into joints during acute flares. These drugs work rapidly in reducing symptoms and erosions, yet the side effects limit long term use (19). Lastly, biologic DMARDs, which are proteins designed to target specific cytokines or their cell receptors (such as TNF-α antagonists) are excellent in reducing symptoms and work well for patients who have failed DMARD therapy. Biologics are very expensive, and although a wide range of biologics are now available in South Africa, their use may be limited in developing countries such as South Africa.

There are many approaches to the treatment of RA, yet the best success is seen from using an aggressive approach (triple DMARDs, usually using methotrexate as an 'anchor drug' in combination with prednisone, with gradual reduction in DMARDs and withdrawal of prednisone until remission is achieved) following early diagnosis (9). Current treatment strategies aim to achieve remission (a disease free state). This requires the use of a treat to target approach, whereby absolute indices of disease activity (such as those derived from the SDAI, CDAI, DAS-28) are used to quantify remission (8). Thus, treatment plans should focus on early, aggressive treatment, a treat to target approach using one of the abovementioned indices in order to target remission or normal functional status, defining the extent of joint damage, followed by optimisation of the therapy for the individual (8).

1.4.2 Non-pharmacological Treatment and Surgery:

Treatment of RA requires a multidisciplinary approach. Patients may be offered joint protection education, physical therapy and nutritional advice, as well as physiotherapy, occupational therapy and podiatry treatment as a means to control their symptoms.

Physical activity has been used as a treatment strategy for RA since the 1950's (39), yet there is still conflicting evidence with regards to the types of activity that should be undertaken, as well as the effects of these activities on RA disease progression. Furthermore, clinicians do not often prescribe physical activity as a means of treatment to their patients. The types of exercises prescribed are generally range of motion and stretching exercises that aim to improve joint mobility; as well as strengthening exercises to improve muscle strength and counteract muscle atrophy. This concept will be expanded on in Section 1.8 and Section 1.10.

Surgery is usually reserved for severe joint damage (9), and as a means to decrease severe pain and to improve functional ability of joints that have severe irreversible damage and deformities. In these cases, joint arthroplasty is usually indicated (9). The incidence of surgery for RA in South Africa has been declining since the introduction of the above mentioned aggressive therapy approach following an early diagnosis (19).

1.5. The Burden of Rheumatoid Arthritis in South Africa:

South Africa is a unique setting for the study of RA as it is a developing, upper middle income country with a prevalence of RA as high as the rest of the world (40), juxtaposed with an underdeveloped health care system and a high rate of poverty, as

well as a high prevalence of many infectious diseases that generally take priority over non life-threatening diseases such as RA.

Epidemiological studies conducted in the 1970s in a Black urban Johannesburg community revealed the prevalence of RA to be unexpectedly high at 0.9% (40), whilst prevalence in rural Black South Africans is lower; between 0.12-0.67% (26). Although the prevalence of RA is relatively low in rural Black South African populations, the prevalence in urban Black South Africans is similar to that of Caucasian populations (40), and European and American Black populations (41). Furthermore, RA disease in urban Black South African populations was found to be similar to the polyinflammatory arthritis found in Caucasian populations, rather than the mild RA often seen in rural South African populations (40). Some studies have however shown that severe RA disease cases are not uncommon in rural Black South Africans (42). While the incidence of RA seems to be decreasing in the United States and Western Europe, the incidence of RA is rising in Africa (43). Black populations have been shown to have a greater excess of females with RA, and a younger age of peak onset when compared to White populations (43). Urban Black South Africans were also found to have a very high prevalence of erosive disease, defined as the presence of an erosion or cortical break "in at least three separate joints at any of the following sites: the proximal interphalangeal, the metacarpalphalangeal, the wrist, and the metatarsalphalangeal joints…" (44), specifically present in the hands and feet (40).

All patients with RA are at increased risk for developing tuberculosis (TB), and the incidence of TB in South Africa is amongst the highest in the world (19). Drugs taken to control RA disease further increase risk of development of TB (19). Human

Immuno-deficiency Virus (HIV) prevalence in South Africa, similarly, is amongst the highest in the world with 33% of females between the ages of 25-29 being infected in 2010 (19). Drug therapy for RA is often immunosuppressive, complicating the management of RA patients who are HIV^+. Additionally, little is known with regards to the effects of anti-retro viral therapies (ARTs) on RA disease process, or the effects of RA drug therapy on ARTs. Many South African patients with RA are immunocompromised, resulting in a need for specialised care and personalised drug therapy that most patients will not receive when diagnosed with RA in a developing country (26).

These complications, coupled with the high rate of poverty and underdeveloped health care system mentioned earlier, make the management of RA in South Africa even more complicated than it is in more developed countries, and special attention needs to be paid to these factors when designing disease management interventions within these populations.

1.6. Rheumatoid Arthritis and Bone Health:

The involvement of bone in RA has been described in much detail since the first description thereof by Barwell in 1865 (45). Currently, it is understood that RA patients are predisposed to developing osteoporosis, which is a systemic skeletal disease resulting in low bone mass (46), and are therefore at increased risk of fracture. Fracture risk can be estimated using dual X-Ray absorptiometry scans (DXA), which calculate areal density of bones and then classify values as either normal, osteopaenic, or osteoporotic, based on criteria established by the WHO (46), by comparing values obtained to those of a healthy index population. The hip and spine are the preferred sites for these measurements due to the high predictive value of hip bone mineral density (BMD) for fracture risk.

Osteoporosis in RA can be generalised, (affecting the axial skeleton such as the hip and lumbar spine), or peri-articular (affecting local areas of inflammation such as the hand joints) in nature. The increased risk of developing osteoporosis is attributed to multiple factors: namely the presence of circulating pro-inflammatory cytokines, the decreased mobility of these patients, resulting in a sedentary lifestyle, as well as certain medications taken to treat the disease such as corticosteroids. There are multiple factors that affect the degree of loss of bone density in patients with RA (see Figure 1.3). Studies have shown that the majority of bone density loss in RA occurs in the first six months of disease (47). Furthermore, patients with higher disease activity have been shown to exhibit greater loss in BMD, and higher indices of bone turnover. Also, levels of mobility and function have been correlated with BMD, as have age, stature, and sex (48-49).

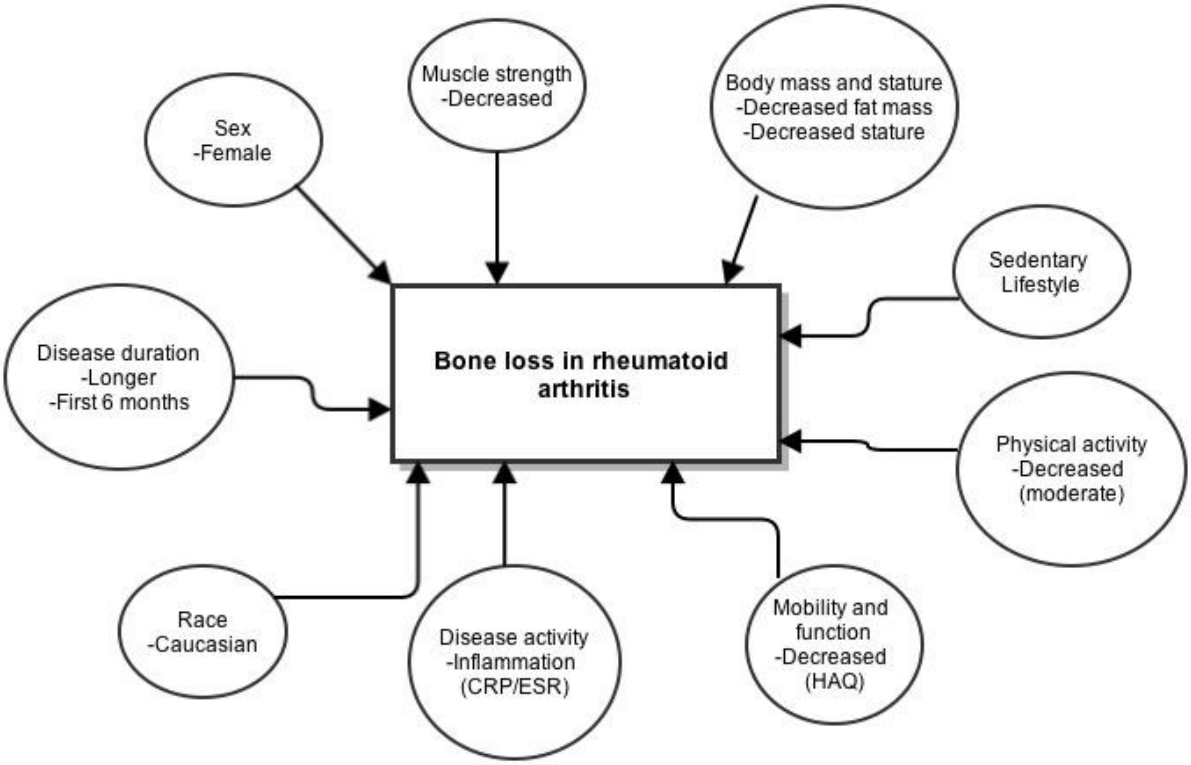


Figure 1.3. Factors that have been documented to affect the degree of bone loss in rheumatoid arthritis in the literature.

It is natural for bone to model and remodel throughout life according to the stresses and strains placed on the bone. Modeling, which refers to the change in shape and structure of a bone, occurs from childhood up to early adulthood, whereas remodeling occurs continuously throughout life. Bone remodeling is dependant on the coupled interaction between bone deposition by osteoblasts and bone resorption by osteoclasts. These cells are highly sensitive to strains and stresses within the bone matrix, and are activated and stimulated to proliferate or apoptose accordingly in response. This process is controlled by receptor activator of nuclear factor-κβ ligand (RANKL) and its permissive factor macrophage colony stimulating factor (M-CSF) which is secreted by local osteoblasts (Figure 1.4). Receptor activator of nuclear factor-κβ ligand binds to its receptor – RANK, on the surface of osteoclast precursor cells in order to stimulate their differentiation into mature osteoclasts, known as osteoclastogenesis. Conversely, osteoblasts secrete osteoprotegerin (OPG), a decoy receptor that binds to RANK and prevents binding of RANKL, therefore inhibiting osteoclast formation and promoting osteoclast apoptosis. Osteoblasts, on the other hand, are highly sensitive to shear stresses and strains within the fluid matrix of bone, and are activated and stimulated to proliferate in response (50).

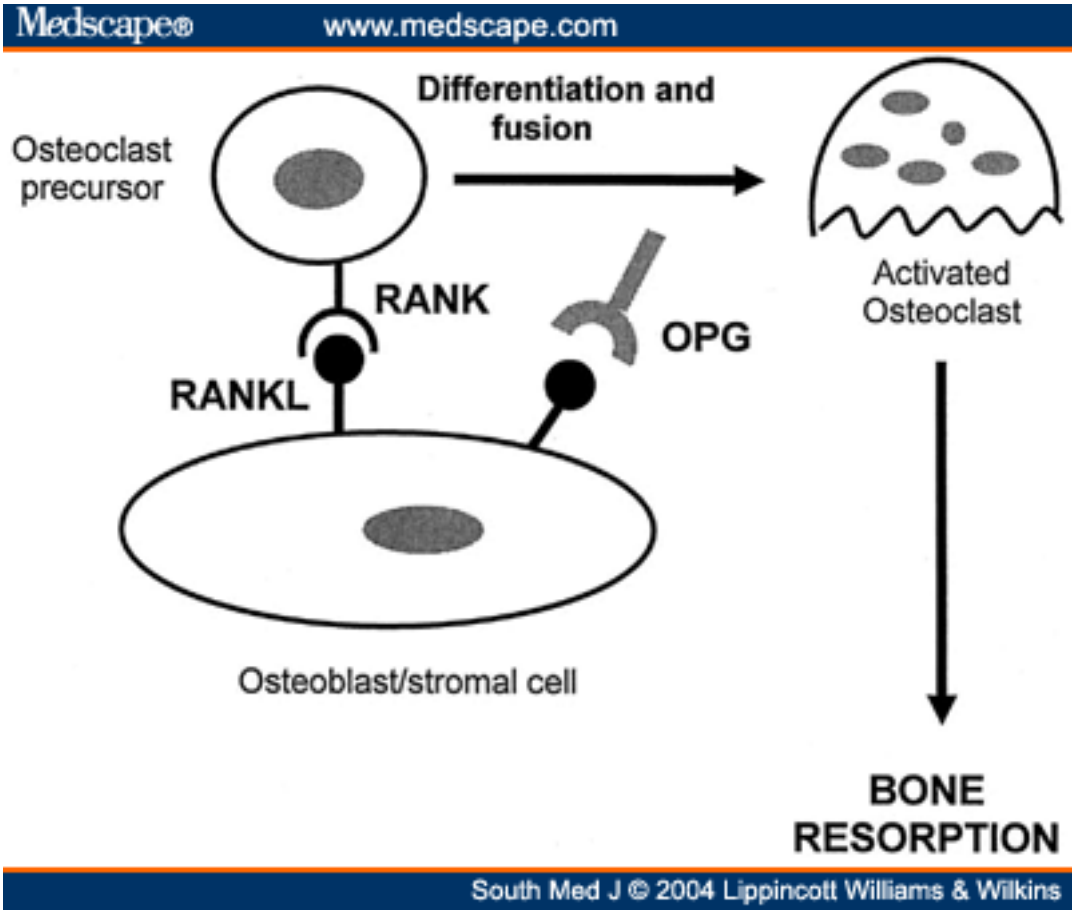


Figure 1.4. Schematic overview of the RANKL/RANK/OPG system that mediates bone modeling. Taken from Coetzee and Kruger in 2004 (51)

The mechanism whereby RA results in bone loss is dependant largely on these systems. Inflammation causes bone loss through the upregulation of RANKL and RANK via pro-inflammatory cytokines, like IL-1, IL-6 and TNF, as well as through regulation of osteoclastogenesis via the modulation of M-CSF. Synovial tissue contains fibroblasts that produce protein for RANKL, and the T lymphocytes within synovial tissue express RANKL on their surface. The rheumatological synovium and inflammatory cytokines present therefore sustains an osteoclastogenic environment. Furthermore, TNF-α, which is elevated in RA, both promotes osteoclastogenesis and inhibits osteoclast apoptosis (50).

This increase in osteoclastogenesis and consequent bone loss evident in RA is further amplified by the decreased mobility and sedentary behaviour that these patients

exhibit. Wolff's law, which has been described over a century ago, states that the skeleton transforms it's mass and morphology according to individual activity levels and forces placed upon the bone (52). Furthermore, Frost's mecahnostat theory, derived in 1964, states that each bone has a specific strain threshold, and that in order for that bone to be remodeled, the minimum effective strain must be placed upon it (53). A sedentary individual does not place sufficient strain on the skeleton, and bones are thus remodelled in a direction that promotes bone loss. Patients with RA are therefore at increased risk of osteoporosis due to inflammatory processes inherent to their disease, and the consequent effect of a sedentary lifestyle (50).

The additional factor contributing to osteoporosis in RA is the drug therapy used to treat the disease. Glucocorticoids are commonly used to treat inflammatory diseases such as RA, yet are associated with the development of osteoporosis and fractures (54). Glucocorticoids affect the function and replication of osteoblasts, as well as increase apoptosis of mature osteoblasts, and inhibit apoptosis of osteoclasts. Glucocorticoids also increase expression of M-CSF and RANKL, as well as decrease expression of OPG, and inhibit calcium uptake, therefore promoting bone resorption (50).

These factors predispose patients with RA to developing osteoporosis and therefore to increased risk of fracture. A study conducted on a cohort of female patients with RA in Oslo, has shown that overall risk of osteoporosis was two-fold higher in these patients than in the general population, and that this risk was higher in patients who were older, had a longer disease duration, were post menopausal, had higher levels of disability, had a positive RF, and had a low body weight (55). Fracture risk is greater

with osteoporosis of the hip and the spine, and incidence of osteoporosis at these sites is between 15-20% in patients with RA (50).

Bone health in RA can be modified using treatments designed to increase bone mass (such as bisphosphonates, vitamin D and calcium, TNF inhibitors and biologic DMARDs), treatments to decrease RA disease activity (as are discussed in Section 1.4.), or by increasing physical activity sufficiently to increase bone loading and remodeling. Regular exercise can increase bone strength by increasing bone size, shape, and density (56) This concept will be explored in more detail in Sections 1.8 and 1.10

1.7. Rheumatoid Cachexia and Sarcopenia:

Rheumatoid cachexia is a term used to describe the concurrent decreased body mass, increased resting energy expenditure and increased whole body catabolism that often occurs with RA (57). The end result of cachexia is skeletal muscle wasting, and increased fat mass. The term 'cachexia' was first described by Sir James Paget in 1873, and was derived from the Greek term meaning 'bad condition' (58-59). Recent definitions of cachexia explain the condition as a metabolic syndrome that is characterised by loss of muscle (sarcopenia) with or without loss of fat mass (58). Rheumatoid cachexia, unlike classic cachexia, which is observed in only 1-13% of RA patients, usually presents with preserved or increased fat mass (60). Rheumatoid cachexia occurs in 10-20% of patients with well controlled disease, and around 38% of patients with active disease (60), and is associated with increased mortality and morbidity (59). The hypermetabolism and protein catabolism seen is associated with the increased pro-inflammatory cytokines such as IL-1 and TNF-α, as well as with decreased peripheral insulin activity, and decreased physical activity levels (59).

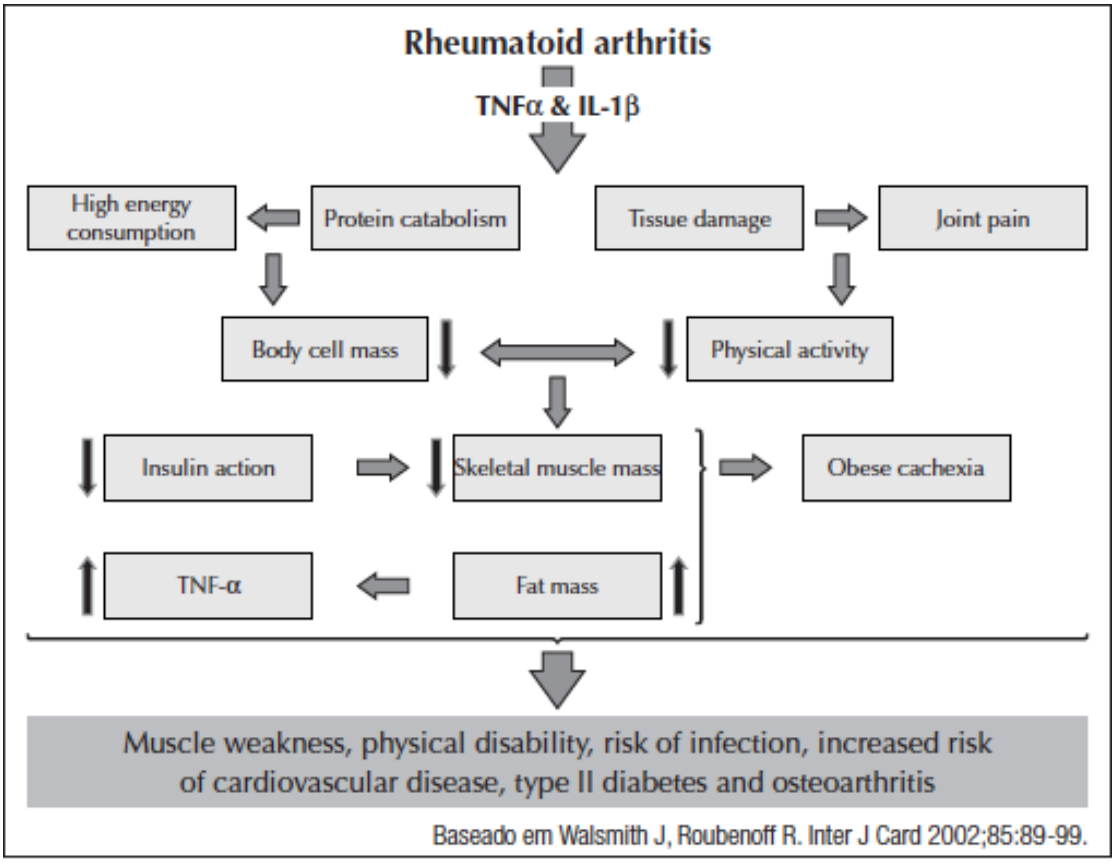


Figure 1.5. Relationship between rheumatoid disease process and cachexia in rheumatoid arthritis. Taken from da Rocha et al in 2009 (61)

The decreased body cell mass (BCM)- consisting of muscle mass, visceral mass such as serum proteins, erythrocytes, granulocytes, lymphocytes, liver, kidney, pancreas and heart, and immune cell mass- which occurs in cachexia can result in death due to decreased muscle strength and altered metabolism. Cachexia also increases susceptibility to infection, which is already 2-5 times greater in patients with RA compared to the general populace (59). Roubenhoff et al (62) showed that RA patients have a 15% decrease in BCM, which is more than one third of the maximal survivable loss of BCM (58). Sarcopenia in RA is a manifestation of cachexia, yet still carries adverse outcomes of its own such as disability, lower HRQoL and death (63), Three effective treatments of rheumatoid cachexia and sarcopenia exist: exercise-, dietary- and pharmacological interventions. Regular, progressive resistance training has been

shown to be the most effective, nonpharmocological intervention to treat cachexia in RA (59).

Resistance training of sufficient intensity, duration and dose can increase fat free mass in patients with RA (64) and has been shown to be able to normalize the accelerated protein catabolism seen in RA due to increased TNF-α (57). Sharif et al in 2011 (65) showed that resistance exercise 3 times per week for 16 weeks, was able to increase resting energy expenditure, endurance, strength, and muscle fiber cross sectional area, as well as decrease pain, and disease activity scores in a case study of one female patient, aged 46. The authors found, however, that resistance exercise was not able to decrease fat mass in this individual, and recommend that some form of aerobic exercise be included in order to maximise the beneficial effects seen.

Increased fat mass often leads to obesity, which is considered a pro-inflammatory state (66), and in order to counteract this; adipocytes secrete adiponectin, which is an anti-inflammatory adipokine (67). Patients with RA have more circulating adipocytes than healthy individuals (57), indicating that obesity in RA may have a protective role in terms of inflammation and disease activity. Indeed, having a low body weight is one of the most predictive indicators of developing more active disease, and poor radiological outcome in RA (58). However, increased fat mass combined with decreased lean body mass and a sedentary lifestyle is a major risk factor for developing cardiovascular and metabolic diseases, as well as osteoarthritis (57). Aerobic exercise can decrease the risk of cardiovascular disease (67), and as such, after twelve weeks of aerobic exercise training female South African RA patients have been shown to have significant improvements in cardiac autonomic function (68). Exercise interventions, including resistance as well as aerobic exercise, would

therefore be beneficial in reversing or slowing down the progression of rheumatoid cachexia and sarcopenia, as well as their associated complications.

1.8. Physical Activity and Rheumatoid Arthritis:

Pain control in RA is important in itself, but also to improve quality of life and increase functional ability. Physical activity as a term is often used broadly, and it is important to define the term in the context of this thesis. Physical activity involves all body movements, and includes structured, planned exercise, as well as leisure activities, household chores, occupational activities and ambulatory movements (69). Physical activity interventions generally involve increasing structured exercise via an exercise programme. Habitual physical activity, as used in this thesis, refers to ambulatory movement (simply moving around) and day-to-day activities such as household chores and possibly occupational activities, as well as travel. Habitual physical activity can include structured exercise; however in the case of patients with RA, it often does not.

Physical activity has been promoted as a form of treatment for RA since the 1950's (39), and randomised controlled trials studying the effects of physical activity interventions in RA have been conducted since the 1970's (70). Habitual physical activity, on the other hand, has been shown to be lower in patients with RA in comparison to healthy controls when measured subjectively, yet there is a lack of definitive, objectively measured evidence to prove this relationship (69). Furthermore, there has been little research into the effects of increasing habitual physical activity levels on disease activity in RA. Much of the research in this field has focused on exercise interventions within the RA population, and here most authors have found physical activity to either have no effect on pain levels or joint scores (71), or to

slightly improve joint counts over time (72), increase muscle strength, functional status, balance, flexibility of joints, and to decrease pain (73). The most recent reviews of all the randomised controlled trials using a physical activity intervention in patients with RA are considered in Section 1.10. Included in these reviews are trials that were conducted from as early as 1975 using aerobic (cycling, dance, aquatic and walking and running), as well as resistance training interventions. These studies revealed that exercise is generally effective in reversing joint damage, and in improving functional capacity, strength, aerobic capacity, and sometimes pain. Resistance training has been shown to improve strength, muscle mass, and functionality (74), to improve certain measures of cardiac health, HRQoL, disease activity and functional capacity (68, 75).

Although physical activity interventions are evidently beneficial in RA, it is unclear how increased habitual physical activity affects disease activity, and whether it can improve functional ability (69). Roubenhoff et al (2002) are of the opinion that there is no evidence that controlling inflammation and joint pain will reverse the sedentary habits of patients with RA (57). Henchoz et al (2012) later showed that patients with RA who had greater habitual physical activity levels, as assessed via physical activity questionnaires, exhibited better disease activity scores (76).

Habitual physical activity is difficult to assess as an outcome measure of disease activity due to the lack of objective measurement tools available. Questionnaires and recall diaries are commonly used in research, but are subjective (77). Furthermore, it is often difficult for patients to recall their activity levels accurately, especially for light to moderate activities (78). Accuracy in these subjective measures relies on patient fluency in the English language as well as compliance, and as such

questionnaires cannot necessarily be used reliably in all population groups (particularly in South Africa). Nevertheless, physical activity questionnaires are currently being used as a subjective means to 'quantify' physical activity levels in patients with RA (76, 79), and these studies consistently report that habitual activity levels are significantly lower in patients with RA as compared to healthy populations. The lack of an objective assessment tool to measure physical activity in RA (or any other chronic disease), however needs to be addressed in order enable an empirical comparison of these physical activity levels.

1.9. Accelerometry:

Accelerometry is an objective means of measuring physical activity. Accelerometers measure the acceleration of the limb to which they are attached by detecting low frequency (0.5-3.2 Hz) gravitational forces (0.05-2.0g) (80). Acceleration is thought to be directly proportional to muscle forces generated, and therefore to energy expenditure (78). This theory along with an inbuilt algorithm allows for the conversion of energy expenditure into activity counts, which are generated every minute, or in specific time intervals as specified by the user. These counts can be classified into thresholds indicating sedentary, light, moderate or vigorous intensity levels (78). Sedentary activity is defined as any activity which does not increase energy expenditure above that of resting (4); while light, moderate and vigorous activities raise energy expenditure to various degrees above resting levels. These terms are further defined in the Operational Definition of Terms.

Actical accelerometers (Respironics Inc, Murrysville, USA) are small, unobtrusive and comfortable. The accelerometer device has been shown to be most accurate when placed on the part of the body where the motion occurs, and studies have shown the

hip to be the only place able to predict free living activities at all intensity levels, with the wrist and ankle being second and third best respectively (80). Figure 1.6 shows a typical graphical output from an Actical accelerometer.

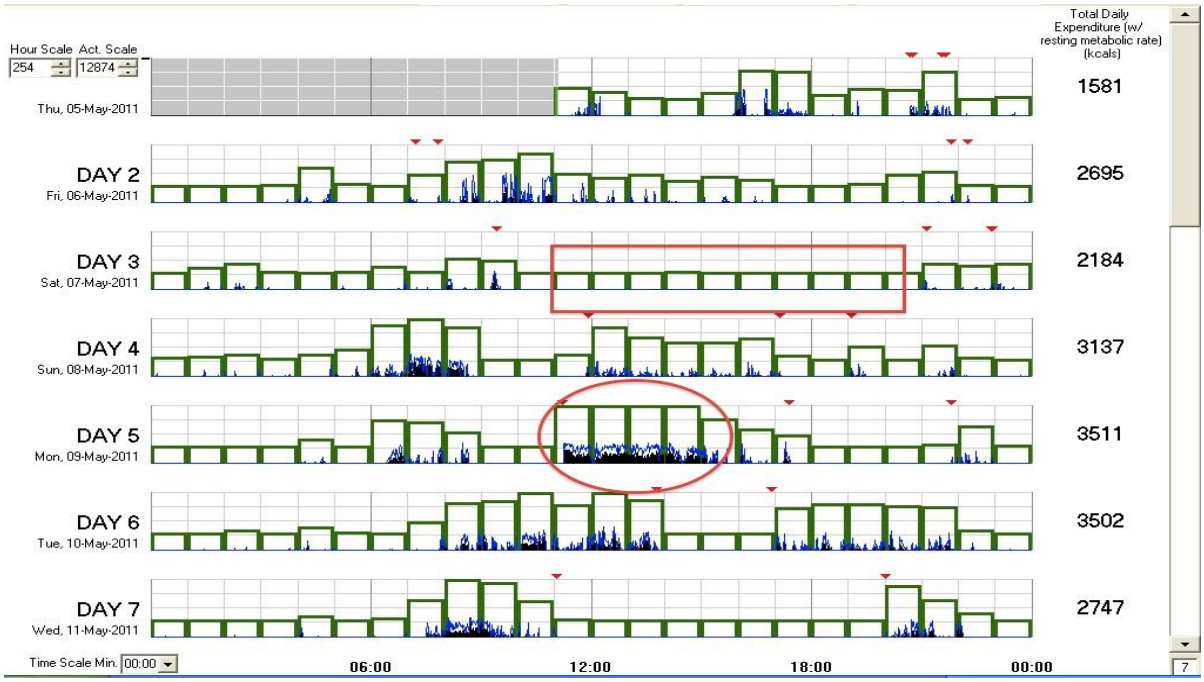


Figure 1.6. Accelerometer data from an Actical worn on the hip over seven days. Data on the right shows total energy expenditure per day in kcal. Spikes in data indicate peaks in activity counts during the day, while the blocks indicate energy expenditure during the day. The circle highlights a period of particularly high activity for this participant, where activity counts are high as is the energy expenditure. The rectangle highlights an area of very low activity with low activity counts and energy expenditure as basal level only.

Accelerometry has potential advantages over self-reported measures of physical activity, such as being able to track intensity, duration and frequency of an activity without relying on patient recall (81). Omnidirectional accelerometers such as the Actical, although being able to more accurately predict low level activity levels that unidirectional accelerometers, still have certain limitations, such as slightly underpredicting light activity and not being able to accurately predict energy expenditure not associated with acceleration (in which case a heart rate monitor is better advised) (82). Despite these limitations, accelerometers can detect varying levels of activity, being able to detect activities of a low intensity and movement in multiple planes better than other accelerometers (80), and showing better inter- and

intra-device reliability than other accelerometers (83). Accelerometers would, as such, be ideal for measuring ambulatory physical activity levels in patients with RA, who are generally sedentary and where most movement is functional and of low frequency and intensity, and therefore unlikely to be reported accurately using self report measures. Accelerometers could also be ideal for measuring physical activity levels in South African populations where not all patients are fluent enough in English to be able to complete extensive activity questionnaires accurately. The accuracy of accelerometers is not dependent on language, making it ideal for use in a developing country such as South Africa.

Few studies have been done using accelerometers to measure physical activity levels in patients with chronic disabling conditions such as RA (80), and none have been done in Black South African women with RA, even though these patients may not be able to accurately report their activity levels subjectively using questionnaires. Of the few studies that have been done, one used a Dynaport monitor to quantify the amount and intensity of physical activity in patients with RA, and the ambulatory monitor measurements were correlated with physical activity, functional status and disease activity in these patients (78). In another study, an ActiGraph accelerometer worn on the hip of RA patients for a week was able to measure physical activity in these patients, although this study did not examine the associations between habitual physical activity and disease activity, and the authors suggest that it is important to have accurate thresholds for activity levels in chronic pain patients such as these (84). Accelerometers have been used in RA in order to determine the effects of 'activity pacing' on habitual physical activity levels (85). The authors of this study found that activity pacing was associated with decreased habitual activity levels in these patients. They also found that physical activity levels were over-estimated when using

questionnaires, in comparison to the objectively acquired accelerometer data. Lastly, Acticals were used in a cross-sectional study in order to determine which factors predispose RA patients to being inactive (86). The authors found that 42% of patients were inactive, and that the strongest predictors of inactivity were lack of motivation and belief related to physical activity. There has, however, been no work done comparing habitual activity levels in RA patients to healthy subjects, or assessing the relationship between habitual physical activity levels and disease activity in RA.

The Actical accelerometer has also been used to measure physical activity levels in patients with other painful conditions such as primary dysmenorrhoea and fibromyalgia. In women with primary dysmenorrhoea, who subjectively report similar symptoms to patients with RA, such as decreased physical activity and functional ability, the Actical was able to detect decreases in physical activity in response to changes in pain levels (77). Patients with fibromyalgia and chronic fatigue syndrome have some symptoms similar to RA, such as pain, fatigue, depression, tender joints and subjectively reported decreases in physical activity (23). In these patients, accelerometry detected reduced levels of peak activity in comparison to healthy, age-matched controls, and these measurements were also correlated with subjective measures of physical activity (23). Lavie et al (1992) studied patients with fibromyalgia using the Actical accelerometer to measure not only daily physical activity and habitual behavior, but also sleep patterns, and found accelerometry data to correlate well with sleep logs and polysomnography, the gold standard for sleep measures (87). Similarly, Pruitt et al (2008) conducted a study in RA using actigraphy to measure their sleep quality, and found that movements detected during sleep using actigraphy were well correlated with poor sleep quality defined using polysomnography (78).

Accelerometers offer a potential method of objectively and unobtrusively measuring physical activity, whether functional or recreational. Patients with RA are generally sedentary, and most activity undertaken is functional, and thus of low intensity. Accelerometers could potentially be a tool for measuring these low intensity activities accurately by overcoming the inaccuracies present in evaluations done by means of subjective questionnaires, thus providing a means for clinicians to determine daily physical activity levels and functionality in RA patients.

1.10. Exercise Interventions for Rheumatoid Arthritis:

Exercise interventions of various modalities have repeatedly been shown to have beneficial effects on most outcomes in RA (88). That being said, there is still a lack of definitive guidelines for physical activity interventions in RA. Meta-analyses have been conducted to assess the effects of various exercise interventions on RA, yet due to the vast differences in intervention types, duration, intensity, population samples, and outcomes measured; the most effective means of delivering an intervention to this population remains to be established. It is likely that interventions will need to be tailored specifically for age, disease duration, functional disability and radiographic joint progression, amongst other things. In spite of these limitations, exercise interventions show promising results in improving many facets of RA. Table 1.3 below, (modified from those of Cairns et al in 2009 (89), Metsios et al in 2008 (90), and Baillet et al in 2010 (91)), summarises the current literature on exercise interventions in RA. Although not exhaustive, this table includes all the randomised controlled trials (RCTs) conducted between 1975 and 2013, as well as some pertinent cross sectional and non-randomised longitudinal trials which have assessed the effects of various types of exercise interventions (aerobic, strength, or combinations thereof) in patients with RA, in comparison to a control group (either standard care, routine

exercise therapy, standardised range of motion (ROM) exercises, or habitual daily activities). From this table it is evident that, although exercise has been used in RA for many years, definitive guidelines are not yet available.

Table 1.3. Exercise interventions for the treatment of rheumatoid arthritis

Study (Author, year)	Participants (Exercise vs. Control)	Exercise Intervention	Control group activities	Duration	Outcomes measured	Results (Significant improvement in exercise group vs. control group)
Ekblom et al, 1975	23 vs. 11	Cycling 50-70% HR max 5 days per week twice daily	Rehabilitation programme	6 months	Aerobic capacity, pain, muscle strength	Increased aerobic capacity (chronic and acute)
Nordemar et al, 1981	23 vs. 23	Home based cardiorespiratory 70% HR max 30-60 min	Pharmaceutical therapy	4-8 years	Joint damage, walking time, quad torque, CVS fitness	Less joint progression, increased walking ability, and quad torque
Harkom et al, 1985	11 vs. 6	Cycling 70% HR max 3 days per week	Routine activities	12 weeks	V02 max, muscle strength, joint count, functional status	Increased V02 max and decreased joint count
Stenstrom et al, 1991	30 vs. 30	Aquatic programme 1 day per week 30-40 min	Standard medical treatment	4 years	Activity, grip strength, functional status	Increased activity and grip strength, less admittance for hospital care
Baslund et al, 1993	12 vs. 12	Cycling 80% HR max 2 days per week 45 min	Current activities	3 months	Functional capacity, strength, ESR, joint counts, morning stiffness	Functional capacity and strength increased

Hansen et al, 1993	45 vs. 15	Aquatic programme 3 days per week 45-90 min	Normal treatment	2 years	Disease activity and joint damage	No effect
Hansen et al, 1993	60 vs. 15	Home based cardiorespiratory 70% HR max 3 days per week 90 min	Usual care	104 weeks	Morning stiffness, pain, joint count, health assessment, ESR, Hb, x-ray	No effect
Lyngberg et al, 1994	12 vs. 12	Cycling and dynamic strength 50-70% HR max 2 days per week 45 min	Usual care	12 weeks	Joint count, walk time, muscle strength, V02 max, ESR	Left ankle strength increased, functional capacity increased
Stenstrom et al, 1994	42	Dynamic aerobic and strength home exercises 5 days per week	None	12 weeks	Self efficacy, functional capacity, pain, mobility, Ritchie index	Improved pain, self efficacy, mobility, functional capacity and Ritchie index
Noreau et al, 1995	19 vs. 10	Supervised cardiorespiratory dancing 50-70%HR max 2 days per week 15-30 min	Usual care	12 weeks	50 foot walk, aerobic capacity, strength, mood, pain, depression and anxiety	Improved 50 foot walk, strength, endurance, and decreased pain, depression and anxiety.
Hall et al, 1996	69 vs. 70	Aquatic programme or land exercise 2 days per week 30 min	Seated immersion or relaxation	3 months	Quality of life	Physical and psychological benefits

Rintala et al, 1996	18 vs. 16	Aquatic programme 2 days per week 45-60 min	Normal activities	24 sessions	Muscle strength, mobility, aerobic capacity	Increased muscle strength and mobility
Van den ende et al, 1996	25 (in each of 3 exercise groups) vs. 25	High intensity exercise Low intensity group exercise Low intensity individual exercise 3 days per week 60 min	ROM exercise at home	12 weeks	$V0_2$ max, muscle strength, HAQ, joint count, pain, ESR/CRP	$V0_2$ max, joint mobility, muscle strength, swollen joint count (more in high intensity)
Komatireddy et al, 1997	25 vs. 24	Circuit training 3 days per week 20-27 min	Habitual activities	12 weeks	Muscle strength, V02 max, functional status, joint counts	Decreased self reported joint count, night pain, increased strength and anaerobic capacity
Sanford-Smith et al, 1998	24 total	Aquatic programme 70% HR max 3 days per week 25-30 min	ROM and isometric exercise	10 weeks	Grip strength, fitness, ESR, HAQ	Increased grip strength and exercise tolerance, decreased ESR
McMeeken et al, 1999	17 vs. 18	Quadriceps and hamstring training	Normal activities and weekly contact	6 weeks	Muscle strength, HAQ, pain, TUG	Peak muscle torque, pain, HAQ, TUG
Hakkinen et al, 1999, 2001, 2003, 2004 (multiple)	35 vs. 35	Home based dynamic strength 2 days/week 45 min	ROM and stretching	24 months	Muscle strength, BMD, DAS28, HAQ, Larsen score,	Increased strength, improved DAS28, HAQ, ESR, Pain and increased hip BMD

Westby et al, 2000	23 vs. 30	Aerobic dance and strength 3 days per week 45-60 min	Habitual activities and therapy	12 months	Joint count, ESR, BMD, HAQ, fitness	Fitness (questionnaire) Functional capacity
Van den ende et al, 2000	34 vs. 30	Supervised isometric and isokinetic and cycling 60% HR max 3 days per week 15 min	ROM exercise and isometric	30 days	Swollen joint count, muscle strength	Muscle strength, decreases disease activity (both groups)
De jong et al 2003, 2004 (multiple)	151 vs. 158	Cycling, circuits, games 70-90% HR max 2 time/week 75 min	Usual care	104 weeks	BMD Larsen score Muscle strength, DAS28, HAQ	Increased functional ability, slowing of loss of BMD at hip, No radiographic progression of hand and feet
Bilberg et al, 2005	22 vs. 27	Moderate pool exercises 2 time/week 45 minute 70% HR max	Normal activities	12 weeks	V02 max, SF-36, Physical function	Increased muscle function and endurance
Munneke et al, 2005	151 vs. 158	Cycling, circuit, games 70-90% HR max 2 days per week 90 min	Habitual activity	24 months	Radiographic joint change	Accelerated joint damage progression in those with existing damage
Meligoklou et al, 2006	20 vs. 20	Treadmill 60% HR max 2 times per week 20 min	ROM exercise	2 weeks	IGF-1, IGFBP-3, pain, HAQ, ESR, CRP	IGF-1 concentration improved

Van den berg et al, 2006	82 vs. 78	Home based cardiorespiratory exercise 60=80% HR max 5 times per week 10-30 min	Education	52 weeks	Physical activity, quality of life, functional ability, disease activity	No effects
Eversden et al, 2007	57 vs. 58	Hydrotherapy Once per week 30 min	Land exercises	6 weeks	Global impression of change, HRQoL, Health status, HAQ, 10m walk test	Increased impression of change
Neuberger et al, 2007	173 vs. 75	Supervised and home based cardiorespiratory 60-80%HR max 3 days per week 60 min	Usual care	12 weeks	Pain, fatigue, depression, walk time, grip strength	Pain, fatigue and depression decreased in class exercise, walk time and grip strength improved in both groups vs. control
Baillet et al, 2009	25 vs. 23	Supervised cardiorespiratory and conditioning 60-80%HR max 5 days per week 45 min	Education	4 weeks	HAQ, health, HRQoL, joint progression, DAS28, fitness, dexterity	HAQ, health and fitness improved
Lemmey et al, 2009	13 vs. 15	Progressive resistance training 80% 1 Rep max 2 times per week	ROM exercise	24 weeks	Lean body mass, Appendicular lean mass, fat mass, function, disease activity, muscle strength, IGF	Increased lean body mass and appendicular lean mass, and protein, decreased fat mass and trunk fat in both groups, increased strength and 50 foot walk, increased IGF-1, IGFBP-3, decreased cachexia and obesity.

Janse Van Rensberg et al, 2010	19 vs. 8	45 minutes aerobic exercise as well as stretching and strengthening exercises 3 times per week	Usual care	12 weeks	DAS28, HAQ, pain, strength, flexibility and fitness	Increased flexibility, strength, fitness and disease activity in exercise group. Increase in strength and HAQ, and decrease in fitness in control group.
Janse Van Rensberg et al, 2012	19 vs. 18	45 minutes stretching, strength and aerobic exercise 3 times per week	Usual care	12 weeks	Heart rate variability, DAS28	Improved cardiac health (as measured by heart rate variability) in exercise group vs. control group.

HRmax – Heart rate maximum, VO_2 Max – Maximum volume O_2, SF-36 – Short form-36, BMD – Bone mineral density, DAS28 – 28 joint disease activity score, HAQ - Health assessment questionnaire, ROM – Range of motion, ESR – Erythrocyte sedimentation rate, TUG –Timed up-and-go test, CRP – C-reactive protein, IGF – Immunoglobulin factor, CVS – cardiovascular, Hb – Haemoglobin, HRQoL – Health related quality of life, 1 Rep max – 1 repetition maximum.

The meta-analysis conducted by Baillet et al (91) provides cumulative results from RCTs comparing aerobic exercise to either non-aerobic exercise, education or standard care for RA. They conclude that aerobic exercise of various modalities has beneficial effects on HRQoL, functional ability, pain levels, tender and swollen joint counts, and radiographic damage. Certain patient characteristics at baseline were found to influence the outcome; shorter disease duration resulted in increased improvement of pain levels and HRQoL, and lower HAQ scores at baseline resulted in significantly greater improvements in functional ability following an exercise intervention. The design of the exercise intervention also altered the outcomes; HRQoL was only improved following interventions that lasted less than three weeks, and sessions lasting longer than 60 minutes. Supervised exercise influenced HRQoL more so than unsupervised exercise. Lastly, pain scores were only improved following interventions lasting less than three months.

Similarly, based on meta-analysis, Cairns et al (89) concluded that aerobic exercise was able to improve muscle strength, physical function, aerobic capacity, disease activity, and, in one study, hip BMD. Higher intensity exercise imparted greater benefits than lower intensity exercise; and it was evident that a combination of aerobic and strength exercises was needed in order to achieve both increased aerobic capacity, as well as increased strength. Only one study, conducted by Munneke et al in 2005 (92), reported negative effects of aerobic exercise. They observed a worsening of some of the joints of the shoulder and the subtalar joints. Although their study was a retrospective analysis, they cautioned against prescribing aerobic exercises in patients with high baseline radiographic damage.

There is clear evidence for the benefits of exercise for RA. What remains to be determined is how best to refine these interventions for specific subgroups of patients, based on factors like disease duration and extent of erosive damage, whilst still ensuring the feasibility of these interventions within these populations. Specifically, long term aerobic and resistance exercises may not be feasible in our South African RA population for various reasons. Lack of financial resources, which may result in difficulties obtaining standard drug therapy, make implementing supervised alternative or complementary therapy such as exercise improbable. Furthermore, patients may not have the resources to travel to exercise centres frequently, nor are there an abundance of community centres that could be used for these purposes (as is often the case in more developed countries). What is also evident from the literature is the lack of exercise interventions in RA that focus specifically on improving bone health. The risk of osteoporosis, and later development of a fracture in patients with RA is greater than in healthy populations. Devising an exercise intervention that is focussed on increasing bone mass (or even slowing down bone loss or preserving bone density); whilst also improving muscle strength, lowering disease activity and pain, and improving quality of life; would have widespread beneficial effects for patients with RA.

1.11. Whole Body Vibration Therapy in Chronic Disease:

Whole body vibration (WBV) therapy is a mechanism whereby a mechanical vibration platform produces energy via forced oscillation. The vibratory waves are then transferred to an individual via propagation through the feet, legs, trunk and finally, the head (93). Vibration platforms can either be oscillating (moving from side to side, whereby opposite legs are elevated and lowered repetitively), or synchronous

(moving up and down parallel to the ground, thereby creating less movement around the axis). Synchronous plates have been shown to create less movement around the hip and spine (94), as well as to exert greater osteogenic effects on the trunk. These plates are therefore potentially safer in patients with joint, muscle, or nerve disorders. An erect posture while standing on the plate further increases transmissibility through the hip and spine (94). Vibration plates can vary in the force generated through alteration of the frequency (measured in Hz and defined as the number of complete up-and-down cycles per second) and amplitude (measured in mm and defined as peak to peak displacement of each cycle) of the vibration (95). Although certain amplitudes and frequencies have been shown to impart deleterious effects on humans, specifically through occupational exposure; low magnitude (1-10mm and 15-60Hz) vibration has been shown to be a safe and effective means to exercise musculoskeletal structures (96).

Whole body vibration therapy is increasingly gaining popularity as a means to increase bone mineral density in healthy subjects, as well as patients with physical diabilities. For the purposes of this thesis, the literature review will focus on WBV therapy as an exercise intervention in chronic musculoskeletal diseases. Whole body vibration therapy has been used in a multitude of musculoskeletal diseases, with varying objectives. These objectives primarily include attempting to improve balance, bone mass, muscle strength, neuromuscular performance, flexibility, pain, stiffness, depression, mobility, and gait; and WBV protocols vary depending on the desired outcome. Table 1.4 below (modified from Wysocki et al (93), Pang et al (97), and Chanou et al (98)), summarises some of the most recent and pertinent RCTs on the use of WBV therapy in any chronic musculoskeletal disease. Excluded from this table

are studies where WBV has been used in healthy populations or children; or where WBV therapy has been used to treat other diseases or outcomes not relevant for the purposes of this thesis.

Table 1.4. Whole Body Vibration therapy in the treatment of chronic musculoskeletal disease: protocols and results

Study (Author, year)	Condition treated	Sample size	Frequency (Hz)	Amplitude (mm)	Duration (min/day)	Days (per week)	Protocol	Outcome measured	Results
Iwamoto et al, 2005	Osteoporosis	50	20	Not reported	4	1	12 months WBV therapy plus drug therapy vs. only drug therapy	Hormonal secretion, bone density, pain	Decreased pain in WBV groups vs. control group
Gilsanz et al, 2006	Osteopaenia (young individuals with spinal fracture)	48	30	Not reported	10	7	48 weeks WBV training vs. control group	BMD, body composition	Increased cancellous and cortical bone, increased paraspinous muscle mass in WBV group vs. control group
Alenthorn-Geli et al, 2008	Fibromyalgia	36	30	2	18	2	6 weeks static and dynamic exercise on WBV plate vs. sham protocol vs. control	Pain, fatigue, stiffness, depression	WBV group decreased pain and fatigue more than other two groups
Moezy et al,	Anterior	23	30-50	2.5-5	4-16	3	4 weeks	Proprioception,	Increased

2008	cruciate ligament surgery						WBV exercises vs. no exercise in conjunction with standard physical therapy	balance	stability in WBV group vs. control group
Ruan et al, 2008	Osteoporosis	116	30	5	10	5	24 weeks WBV therapy vs. control group	BMD, BMI, back pain,	Increased hip and spine BMD and decreased back pain in WBV group vs. control group
Alenthorn-Geli et al, 2009	Fibromyalgia	24	30	2	18	2	6 weeks static and dynamic exercise on WBV plate vs. sham protocol	Hormonal secretion Insulin-like growth factor	No changes evident in either group
Trans et al, 2009	Osteoarthritis	52	24-30	Not reported	3-5	2	8 weeks stable platform WBV vs. balance board WBV vs. control	Isokinetic knee extension, isometric flexion torque, proprioception	Stable platform increased isokinetic knee extension and flexion torque more than controls. Balance board increased knee

									proprioception more than controls.
Gusi et al, 2010	Fibromyalgia	36	12.5	3	3	3-6	12 weeks WBV therapy vs. control	Balance, HRQoL,	HRQoL preserved in WBV group yet decreased in control group
Johnson et al, 2010	Total knee arthroplasty	16	35	2-5	2-18	3	4 weeks static and dynamic exercises on WBV plate vs. standard resistance exercise all in conjunction with physical therapy	Strength, mobility, pain, range of motion	No differences between two groups
Prioreschi et al, 2012	Exercise induced osteopaenia and osteoporosis	15	30	3	15	3	10 week intermittent WBV vs. control group	BMD	Increased hip BMD and maintained spine BMD in WBV group vs. control group.

WBV- Whole body vibration, BMD – bone mineral density, HRQoL – Health related quality of life, BMI – Body mass index.

The ability of WBV therapy to improve the above-mentioned outcomes is of great interest; particularly the ability of WBV to increase or maintain BMD. Studies conducted in postmenopausal women (99), as well as healthy populations (96), and athletes with low BMD (100), have shown WBV therapy to improve BMD, particularly at the hip and spine (101-102). Although the exact mechanisms whereby WBV therapy increases BMD are not entirely clear, it is likely that there are multiple mechanisms at play. Whole body vibration has been shown to activate fluid flow in the canaliculi and lacunae of bone matrix in rats (103), in a manner proportional to loading frequency. This fluid flow creates shear stress on the plasma membrane of osteocytes, bone lining cells, and osteoblasts, which therefore respond accordingly (56). WBV thus activates mechanostransduction in bone, which stimulates osteogenesis (99). Frost's mechanostat theory (104) states that each bone has a specific strain threshold, and that in order for that bone to be remodeled, the minimum effective strain needs to be placed upon it. Anything above this strain will cause new bone deposition, while anything below it with cause resorption of existing bone. Therefore, vibration stimulus must sufficiently load bones in order to increase deposition. Furthermore, muscle forces have been shown to exert the greatest osteogenic stimulus on bone, and the generation of these forces through vibration stimulus is likely a contributor to the skeletal adaptations that occur (94).

The direction of vibration, the frequency and magnitude of load, acceleration, duration of protocol, and body posture on the plate all play a role in the effectiveness of WBV for bone health. Studies have shown that the most effective WBV therapy sessions are 2-20 minutes in duration, and that shorter sessions that incorporate rest periods are the most effective for promoting musculoskeletal adaptations (103). Turner in 1998 stated three 'rules' for bone adaptation, namely: 1) bones respond to dynamic rather than static loading, 2) loading

duration should be short, and 3) that bone cells adapt to regular loading, making them less responsive (53). Hert et al demonstrated in 1971 that bone responds to dynamic loading, due to the increased rate of deformation and fluid flow in the bone matrix. Further, bone cells become desensitized to repetitive loading, losing up to 95% of their mechanosensitivity (105). However, incorporating rest periods between loading periods can return this sensitivity. Vibration set at low amplitudes and higher frequencies (up to 60Hz) have been shown to be anabolic to trabecular bone (106), however protocols in the current literature are varied with regards to exact frequencies and amplitudes used.

Since patients with RA are already at risk for developing osteoporosis, and are therefore at greater risk of fracture; WBV could potentially be a means to treat low BMD, or at least to attenuate the progressive loss of BMD, without the need for a vigorous exercise programme. Exercise interventions in RA are not always feasible, specifically bone loading exercises which need to be dynamic in order to increase bone mass (56). WBV therapy is safe, requires minimal effort and movement, yet still exhibits muscle strengthening effects and stimulates bone loading in a controlled environment.

1.12. The Problem:

The best outcome measures of RA that provide the most definitive assessment of disease activity remain to be elucidated. There is a clear link between physical activity and RA disease activity, yet there are no outcome measures which incorporate objective measurement of physical activity levels, nor is there an understanding of the mechanisms underlying this association. There is also a lack of data regarding the habitual physical activity levels of patients with RA, especially using objectively measured physical activity levels, and there are few comparative studies between healthy control participants and RA patients with regards to physical activity levels. Little is known with regards to the factors that result in changes in

habitual physical activity levels over time, including whether drug therapy affects habitual physical activity levels in any way.

Furthermore, although exercise is prescribed for RA, there is no consensus on the most effective type of exercise for the disease, and many exercise interventions described in the literature are not necessarily feasible in a South African context. Very few interventions focus on increasing bone density as a primary aim, despite the very real risk of fracture in these patients, and the associated implications thereof (social, economical and health related).

The clear link between disease activity and physical activity, compounded by the paucity of knowledge in this area, forms the premise of this research. The objectives of the studies conducted for this thesis were, broadly:

- To assess the potential clinical utility of accelerometry in quantifying habitual physical activity levels and patterns in patients with RA
- To quantify habitual physical activity levels in patients with RA and to determine those factors which affect habitual physical activity and those which are affected by levels of habitual physical activity
- To determine whether WBV therapy would have beneficial effects on functional ability and bone health in patients with RA

1.13 Thesis Framework:

In order to address the broad objectives stated in Section 1.13 above, three main studies were conducted. These studies addressed more specific aims, as follows:

Study 1:

- To objectively quantify habitual physical activity levels in RA patients in comparison to a healthy population
- To ascertain any associations between habitual activity levels and disease activity in patients with RA

Study 2:

- To determine the changes in habitual physical activity levels in patients newly diagnosed with RA in response to commencement of DMARD therapy
- To determine the predictive factors causing the changes seen in disease activity in response to commencement of DMARD therapy in patients with RA

Study 3:

- To determine the associations between habitual physical activity levels and bone health in patients with RA
- To determine the effects of a WBV therapy intervention on functional ability, and bone health, as well as on disease activity and habitual physical activity levels in patients with RA

The results (Chapter 2) of these studies will be presented in the form of the publications that emanated from each specific study, or in the form of the submitted manuscripts in the cases where manuscripts have not yet been accepted for publication. Author contributions and acquiescence forms have been included (Appendix 14). The methodology used in this thesis

will be described in detail within each results section. These publications/manuscripts are as follows:

1. Prioreschi A, Hodkinson B, Avidon I, Tikly M, McVeigh JA. The clinical utility of accelerometry in patients with rheumatoid arthritis. Rheumatology. 2013;52(9):1721-1727. (Appendix 11).
2. Prioreschi A, Hodkinson B, Tikly M, McVeigh JA. Changes in physical activity measured by accelerometry following initiation of DMARD therapy in rheumatoid arthritis. Rheumatology. 2014:53(5);923-6. (Appendix 12).
3. Prioreschi A, Makda MA, Tikly M, McVeigh JA. Higher habitual activity levels are protective of bone health in patients with rheumatoid arthritis. Under review at BMC Musculoskeletal Disorders.
4. Prioreschi A, Makda MA, Tikly M, McVeigh JA. Positive Effects of a 12 week WBV Intervention on Bone Mineral Density and Fatigue are Sustained in a Population with RA. Submitted to International Journal of Bone and Mineral Research.

As well as manuscript describing the protocol used for Study 3 (Appendix 13):

5. Prioreschi A, Tikly M, McVeigh JA. A three month controlled intervention of intermittent whole body vibration designed to improve functional ability and attenuate bone loss in patients with rheumatoid arthritis. Under review at BMC Musculoskeletal Disorders.

The discussion and conclusions section (Chapter 3) that follows these publications/manuscripts will summarise all the results obtained, and integrate the findings in light of the current literature.

1.14. Conclusion:

This chapter has examined the literature with regards to RA, patients with RA in South Africa, bone health in RA, treatments of RA, outcome measures of RA, physical activity in RA and accelerometry, as well as WBV therapy in chronic disease. This chapter concluded by highlighting the gap in the knowledge that I wish to address, and by broadly introducing the objectives of the studies conducted in this thesis.

Chapter 2: Results

2.1. Study 1 – The Clinical Utility of Accelerometry in Patients with Rheumatoid Arthritis[1]

1. Prioreschi A, Avidon I, Hodkinson B, Tikly M, McVeigh JA. The clinical utility of accelerometry in patients with rheumatoid arthritis. Rheumatology. 2013; 52(9):1721-1727

Please note that Table and Figure numbers, as well as citations have been modified from the published version in order to align with the numbering of the thesis.

Abstract:

Objectives: To objectively assess habitual physical activity levels in patients with rheumatoid arthritis (RA) compared to healthy control participants, and to compare these measures to health related quality of life and disease activity in the RA patients. **Methods:** Fifty RA patients (age 48(13) years) and 22 body mass index-, sex- and geographically-matched control participants were recruited. Habitual physical activity was measured using an Actical accelerometer worn on the hip for two consecutive weeks. Patients completed the Short Form-36 (SF-36) and modified Health Assessment Questionnaires (HAQ-DI). Disease activity was assessed using the Simplified Disease Activity Index (SDAI). RA patients were further categorized as more physically active (n=25) and less physically active (n=25) according to their average activity counts. **Results:** The RA group spent more time in sedentary activity than the control group (71% vs. 62% of day respectively, $p=0.002$), and had bimodal decreases in diurnal physical activity compared to the control group in the morning ($p<0.001$) and late afternoon ($p<0.001$). HAQ-DI, when adjusted for age and disease duration, was negatively correlated with physical activity in the RA group ($r=-0.343$, $p=0.026$). The more physically active patients scored better than the less physically active patients on every component of the SF-36. **Conclusion:** Patients with RA lead a significantly more sedentary lifestyle than healthy controls, and show diurnal differences in physical activity due to morning stiffness and fatigue. Higher levels of habitual physical activity may be protective of functional capacity and are highly associated with improved health related quality of life in RA patients.

Introduction:

Patients with RA have been shown to have a decreased health related quality of life (HRQoL) in comparison to the general population (1). HRQoL (which is defined as the physical, emotional and social aspects of life which are affected by a patient's disease or their treatment) is a relevant measure of disease activity according to the WHO (2) and "feeling well" is an important patient outcome, along with management of pain, sleep, fatigue, emotional- and physical wellbeing (1).

The presence of pain limits the ability of patients with rheumatoid arthritis (RA) to function normally, and as a result everyday habitual physical activity levels are reduced (3). Exercise interventions in patients with RA have been shown to improve sense of wellbeing, decrease morning stiffness, improve sleep patterns, and decrease swollen joint counts over time (4), as well as to reduce pain and improve functional ability (5). Increasing levels of physical activity have been shown to be beneficial for patients with RA without having any adverse effects on disease activity (6). Most studies have examined the effects of enforced exercise interventions on RA disease activity, yet surprisingly little is known about the effects of everyday, spontaneous habitual physical activity levels in patients with RA, and whether patients with increased habitual physical activity levels have better disease activity profiles or "feel better". One large study by Sokka et al (2008) did examine self-reported physical activity levels in over 5000 outpatients with RA in over 20 countries around the world and found that over 70% of these patients did not engage in regular physical activity at all. Furthermore, physical inactivity was more prevalent in patients with lower functionality as assessed by the Health Assessment Questionnaire (HAQ) (110). These findings remain to be elucidated using objective measures of physical activity.

Physical activity, as a functional assessment of quality of life is difficult to assess. Questionnaires and recall diaries are commonly used but are subjective (8), and it is difficult for patients to recall their activity levels accurately, especially for light to moderate intensity activities (9). Few studies have been performed on RA patients assessing habitual, daily physical activity levels (10). Two studies have compared energy expenditure levels between patients with RA and controls, (average energy expenditure was found to be lower in RA patients than in controls in both these studies) although both made use of subjective measures of physical activity only (76,79).

Accelerometers are growing in popularity as an objective way to measure physical activity, especially in healthy populations (13), and have been validated using calorimetry and doubly labeled water methods (14). Actical accelerometers are small, unobtrusive and comfortable, and measure acceleration of the limb to which they are attached by detecting low frequency (0.5-3.2 Hz) forces (0.05-2.0g) (13). Acceleration is thought to be directly proportional to muscle forces generated, and therefore to energy expenditure (9). This theory along with an inbuilt algorithm allows for the conversion of energy expenditure into activity counts, which are generated every minute. These counts can be classified into thresholds, indicating sedentary, light, moderate or vigorous intensity levels (9). Accelerometers have advantages over self-reported measures, such as being able to objectively track intensity, duration and frequency of an activity without relying on patient recall (15). Acticals in particular can detect varying levels of activity and movement in multiple planes (10), making them potentially ideal for measuring physical activity in patients with RA, who are generally sedentary and where most movement is functional and of low frequency and intensity, and therefore unlikely to be reported accurately using self report measures.

Accelerometry has already been used to quantify physical activity levels in other rheumatic diseases, such as osteoarthritis (112), and to study knee biomechanics in spondyloarthropathy and RA patients (113). The aims of this study were to assess the potential clinical utility of accelerometry in quantifying habitual physical activity levels and patterns in a group of patients with RA by assessing whether varying levels of habitual physical activity are associated with disease activity and HRQoL; and to compare their physical activity levels to those of a healthy group of control participants.

Participants and Methods:

Participants:

Fifty female patients fulfilling the 1987 ACR classification criteria for RA (18) with a mean age of 48(13) were recruited from the Chris Hani Baragwanath Rheumatology Clinic in Soweto, South Africa (RA group). Participants were excluded if they had any co-morbidities including cardiac, muscle or neurological disorders, that could potentially impact on physical activity, were using any assistive walking devices, or were pregnant. The RA group were compared to 22 control participants (control group) who were matched for mean body mass index (BMI- calculated as weight (kg)/(height(m))^2), race, and sex, and were recruited from the same geographical living area as the RA patients so as to closely match the two groups for socioeconomic circumstances. Ethical approval was obtained from the human research ethics committee of the University of the Witwatersrand (M110430 and M110236), and complies with the Helsinki Declaration. All participants signed written informed consent and were free to withdraw from the study at any time.

Outcome Assessments:

Physical Activity:

Actical accelerometers (Respironics Inc, Murrysville, USA) were worn on a velcro belt on the hip of the dominant leg during the day for two consecutive weeks (the Actical device has been shown to be most accurate when placed on the part of the body where the motion occurs, and studies have shown the hip to be the only place able to predict free living, habitual activities at all intensity levels (13)). Acticals were removed only when the participants were bathing/showering or participating in any water-based activities. Actical data were recorded in one minute epochs and data were reduced by removing only full days of non-wear time (as observed in the counts or as reported by the participants), as well as sleeping time as reported by participants. The remaining data (which included daily activities as well as rest periods throughout the day) are referred to as the "wear period" which was calculated in a similar manner to that described by Semanik et al in 2010 (5). Data for the wear period were divided into thresholds, namely sedentary, light, moderate or vigorous activity according to the activity counts recorded and the inbuilt algorithm calculated by the Actical software (Respironics Inc, Murrysville, USA). Since the participants were found to be extremely sedentary, these data were then expressed as percentage of time spent in sedentary activities on average per day as recommended by Pate et al in 2008 (19). The 95^{th} percentile of the activity counts recorded over the period for each participant was also noted in order to eliminate any outliers in maximal activity counts. Activity counts for each participant were also divided into time intervals throughout the day in order to assess daily habitual physical activity patterns in RA patients (early morning:6am-9am, late morning:9am-12pm, afternoon:12pm-3pm, late afternoon:3pm-6pm, and evening:6pm-9pm), and the average activity counts in each time interval throughout the day were compared between the control group and patients with RA. Participants also completed a physical activity questionnaire after the two weeks stating the type of activities undertaken over the study period, which was used to assess any water based activities that were not recorded by the Actical.

Actical Calibration:

It has been recommended that accelerometers be calibrated according to the types of activities they would be recording (20). All Acticals were calibrated for light ambulatory activity typical of patients with RA by being worn by the same person on the hip of the dominant leg while walking on a treadmill (StarTrac S, Toronto, USA) for five minutes at a standard speed (5km/hour) and with no inclination. The marker button on the Actical was pressed at the start and end of the five minute period and data were recorded as average activity counts per minute over the period. The average activity counts recorded for each person over the two week period was then divided by the calibrated value that was determined for the respective Actical that the participant wore and this new value was used to classify the participants into 'more physically active' and 'less physically active' groups.

Functional Ability, HRQoL and RA Disease Activity:

Before being fitted with an Actical, RA patients completed the Short Form-36 (SF-36) questionnaire, a general assessment of HRQoL comprising of eight categories of health namely; physical function, role physical (the role that health plays on physical function), body pain, general health, vitality, social functioning, role emotional (the role that health plays on emotional function), mental health and reported health, all of which are separated into either composite physical health or composite mental health, and combined to give a total SF-36 score where a higher score indicates a better outcome (21). RA patients also completed a patient global assessment score (PGA), and a modified Health Assessment Questionnaire (HAQ-DI) (22) which is a well validated RA specific assessment of functional capacity where the total score ranges from the best possible result (score of 0) to the worst possible result (score of 3). Patients were all assessed by the same physician (BH) before commencing the study with a tender joint count (TJC), swollen joint count (SJC), and

physician global assessment (MDGA). These, in combination with the C-reactive protein concentration in mg/dL (CRP) and PGA, were used to calculate the composite Simplified Disease Activity Index (SDAI), with cut-offs of <11, >11 and <26, and >26 for low, moderate and severe disease activity respectively (21).

Statistical Analysis:

Unpaired students *t*-tests were used to compare all continuous variables between groups. Pearson's and Spearman's correlations (for parametric and non-parametric data respectively) were used to determine correlations between the objective physical activity counts (which were first log transformed to normalise the data) and subjective questionnaire data as well as disease activity scores within the RA group. A one-way ANOVA was used to assess differences between average activity counts within each category of SDAI. Health assessment questionnaire scores were adjusted for age, as well as disease duration in order to eliminate any confounding variables, and this adjusted mean was correlated with activity counts. The RA group was divided into a "more" physically active group and a "less" physically active group according to the median average activity count value for all the patients over the two week period in order to assess the SF-36 scores using unpaired students *t*-tests to compare the two groups. All statistical analyses were done using STATISTICA v10.0 (Tulsa, OK) and a p-value of <0.05 was considered significant.

Results:

The characteristics of the groups are summarised in Table 2.1. There were no differences between the two groups for any of the variables measured except for age, which was significantly greater in the RA group than in the control group (p=0.018). The mean BMI of

both the RA and control group was greater than 30, categorising participants as obese according to the WHO (23).

Table 2.1. Characteristics of the RA participants and control participants.

	RA group (n=50)	Control group (n=22)	p Value
Age (years)	48(13)	41(8)	0.018 *
Height (m)	1.58(0.05)	1.59(0.11)	0.586
Weight (kg)	80.20(24.67)	77.30(15.61)	0.615
BMI ($kg.m^{-2}$)	32(9)	31(8)	0.639
Disease Duration (months)	99(77)		
SDAI	16(11)		
Tender joint count	4(5)		
Swollen joint count	3(3)		
Physician global assessment	4(3)		
Patient global assessment	5(3)		
C-Reactive protein (mg/dl)	19.68(31.26)		
HAQ index	1.3(0.9)		

All values are mean(SD).
HAQ (Health assessment questionnaire), SDAI (Simplified disease activity index), BMI (Body mass index)
* $p<0.05$

The percentage wear time during the day (mean (SD) of 15(3) hour awake day) spent in sedentary activity is shown in Figure 2.1. Overall, RA patients spent a significantly greater percentage of their day in sedentary activity than the control participants (71(11)% vs. 62(11)%, $p=0.002$), and had a significantly lower value than the control group for the 95^{th} percentile of activity counts recorded (mean (SD) of 22612(12255) counts vs. 37091(17650) counts, $p<0.001$). None of the participants took part in any water based activities.

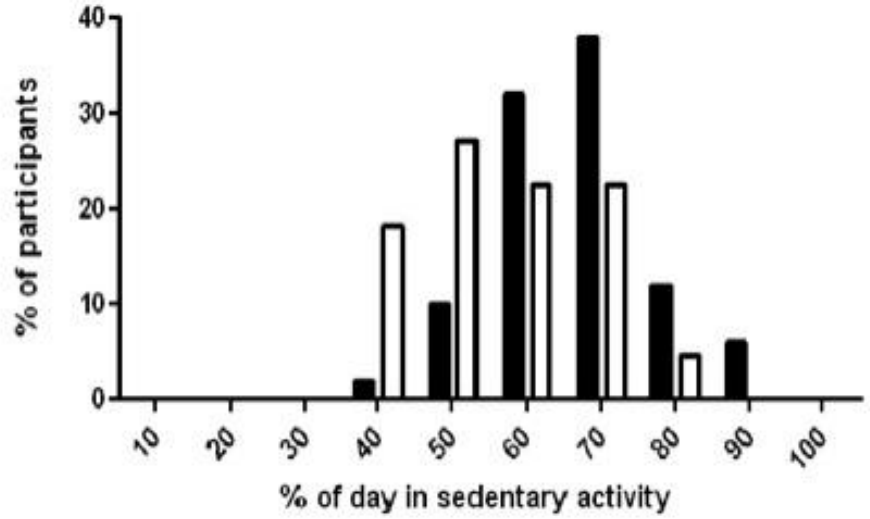


Figure 2.1. Histogram showing the percentage of time spent in sedentary activity between the RA group (black bars) and the control group (white bars).

We assessed how time of day affects physical activity by examining three hourly intervals throughout the day (morning, late morning, midday, afternoon and evening). The average activity counts per three hourly intervals were significantly lower in the RA group compared to the control group for each time category (except for in the evening where there was no difference between the two groups ($p=0.589$)), as shown in Figure 2.2. These differences between the RA patients and controls were greater in the morning ($p<0.001$) and the afternoon ($p<0.001$) than in the late morning ($p=0.033$) and at midday ($p=0.037$).

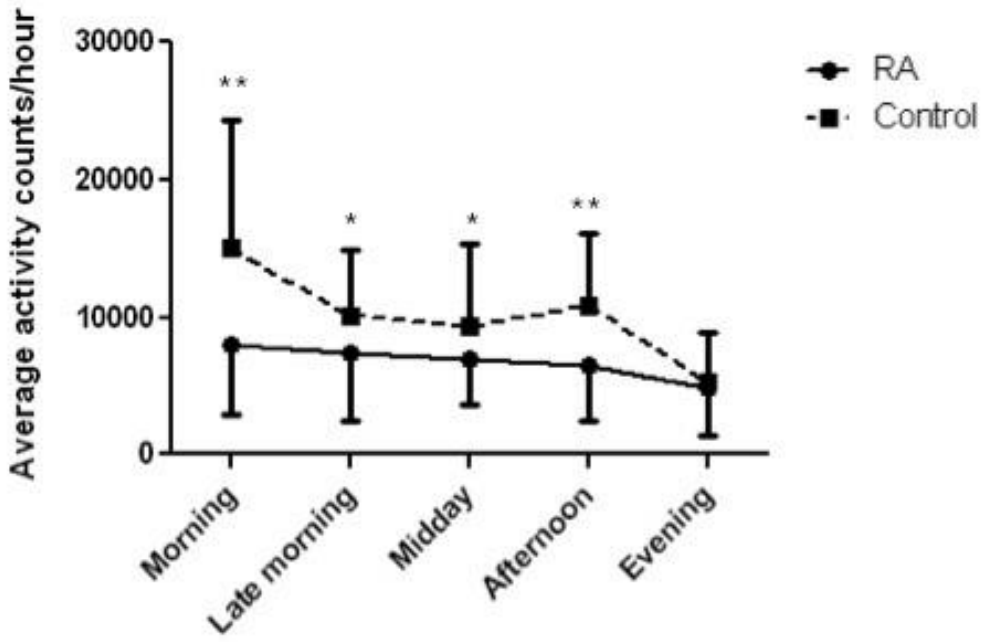


Figure 2.2. Average activity counts per three hourly interval for the RA group (solid line) and control group (hatched line) throughout the day. Morning was calculated from 6am-9am, late morning from 9am-12pm, midday from 12pm-3pm, afternoon from 3pm-6pm, and evening from 6pm-9pm. The control group had significantly higher activity counts than the RA group at all time points except for in the evening.
* $p<0.050$
** $p<0.001$

Table 2.2 shows a correlation matrix between physical activity counts and various outcome measures. Activity counts were negatively correlated with age, BMI and disease duration, and positively correlated with the composite physical health score of the SF-36. There was no correlation between SDAI and physical activity, and there was no difference in the average activity counts of participants who fell into the respective disease classification categories (low to high) of SDAI ($p=0.976$). Rheumatoid arthritis participants had a moderate functional disability according to the HAQ-DI scores shown in Table 2.1 (22). Health assessment questionnaire scores, when corrected for age and disease duration was negatively correlated with physical activity ($r^2=0.117$, $p=0.026$) in the group of RA patients as shown in Figure 2.3.

Table 2.2. Correlation matrix comparing various outcomes to average activity counts per day (when log transformed for normality) within the RA group (n=50)

	Spearman R or r value	p Value
Age	-0.441	0.005 *
BMI	-0.361	0.023 *
SDAI	0.172	0.295
ESR	-0.133	0.419
CRP	-0.028	0.852
Disease Duration	-0.406	0.010 *
SF-36		
Total	0.269	0.097
Composite Mental Health	0.189	0.247
Composite Physical Health	0.326	0.043 *
Physical Function	0.289	0.074
Role Physical	0.173	0.235
Body Pain	0.221	0.177
General Health	0.207	0.207
Vitality	0.187	0.255
Social Functioning	0.117	0.477
Role Emotional	0.100	0.492
Mental Health	0.031	0.853
Reported Health	0.061	0.712

ESR (Erythrocyte sedimentation rate), CRP (C-reactive protein)
Correlations were Spearman's correlations for non parametric data and Pearson's correlations for parametric data as applicable.
* $p<0.05$

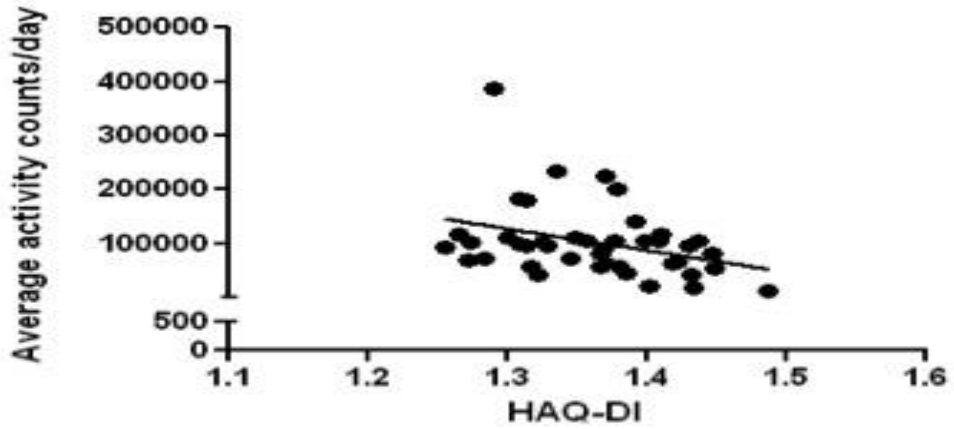


Figure 2.3. Correlation between the average activity counts per day in the patients with RA and HAQ-DI adjusted for age and disease duration (r=-0.343, p=0.026).

There was a wide range of activity counts within the RA group. In order to assess whether SF-36 scores would be different between an 'more active' RA group and a 'less active' RA group, we arbitrarily divided the RA group into a more physically active group and a less physically active group based on the median physical activity count of 1885. The results for the SF-36 between the RA patients (once divided into a more physically active and a less physically active group) are shown in Figure 2.4. Both groups scored poorly (<66), yet the more physically active group scored higher than the less physically active group on every component of the SF-36, and significantly higher for the vitality component (54(17) vs. 45(17), p=0.04), the composite mental health component (53(17) vs. 44(16), p=0.05), the composite physical health component (47(19) vs. 37(18), p=0.05), and the total SF-36 score (49(18) vs. 39(17), p=0.03). The vitality component of the SF-36 was positively correlated with physical activity in the RA patients, and the total SF-36 score trended towards a significant positive correlation with physical activity (r=0.269, p=0.097) as shown in Table 2.2.

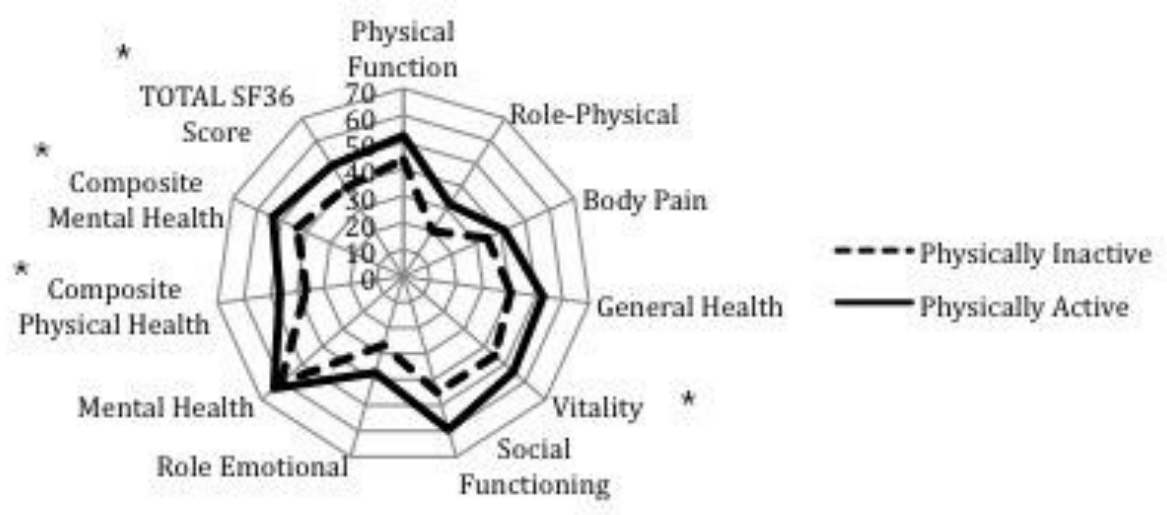


Figure 2.4. Spydergram showing the components of the SF-36 questionnaire for the RA group divided into a more physically active group (solid line) and a less physically active group (hatched line) according to the median activity count value of the whole group. The more physically active group scored significantly higher than the less physically active group for vitality (p=0.034), overall physical health (p=0.05), overall mental health (p=0.05) and total SF-36 score (p=0.03).

Discussion:

We have used accelerometry to quantify habitual physical activity in patients with RA compared to healthy, matched controls. Our data supports the clinical utility of accelerometry as an outcome measure of habitual physical activity in patients with RA as demonstrated by its association with SF-36 and HAQ-DI. In addition, we have shown quantifiable differences in physical activity levels over the course of a day between a group of patients with RA and healthy, matched controls. Patients with RA in the present study were more sedentary and less habitually physically active than healthy, matched controls. An average American adult spends 60% of their day in sedentary activities (24). Our control group spent a similar percentage of their day in sedentary activities, yet our RA group spent almost two hours more each day in sedentary activities than their healthy matched controls.

Daily habitual physical activity patterns for patients with RA were markedly different to that of healthy controls. RA patients were significantly more sedentary than control participants throughout the day except for in the evening, when the two groups converged to a similar average level of activity. Interestingly, the control participants had two peaks in habitual physical activity levels that were not present in the RA group. These occurred in the early morning and late afternoon. The absence of these peaks in activity levels in the patients with RA are likely to be related to two known symptoms of the RA disease, namely morning stiffness of the joints (118) and fatigue, which tends to peak in the afternoon (119). Fatigue is an important barrier to physical activity in patients with RA, and was shown to be negatively associated with subjectively measured physical activity levels in patients with RA (76). The ability of the accelerometer to detect the presence of these symptoms, as well as to differentiate between the two groups through measurement of physical activity, makes it a promising tool in the measurement of RA disease outcomes.

Similar to Sokka et al, we have reported decreased functional ability in patients with RA in association with decreased physical activity levels, but have extended and further unpacked this finding with the use of an objective measure of physical activity. The clinical utility of accelerometry devices could minimise the difficulties associated with language and questionnaire limitations. Functional capacity (as assessed by the HAQ-DI) was shown in the current study to be negatively correlated with objectively measured physical activity in patients with RA. Higher levels of habitual physically activity may have a protective role on functional disability in patients with RA. de Jong et al in 2003 found HAQ scores to decrease (although not significantly) in a group of patients with RA who underwent dynamic exercise training for two years (27). Also, Walker et al in 1999 found HAQ scores to be negatively correlated with ambulatory activity in patients with RA as measured by a Numact activity monitor, which only assesses energy expenditure, calculated from number and vigour of steps taken (28). Henchoz et al in 2012 found that HAQ was not associated with physical activity, yet their study did not assess physical activity objectively. Despite this, all disease-related scores were found to be significantly poorer in sedentary compared with physically active patients (76). We show an association between increased levels of objectively assessed habitual physical activity (using a calibrated activity monitor capable of quantifying intensity and frequency of activity within certain thresholds) and functional ability in patients with RA, supporting the utility of the accelerometer as a complementary outcome measure for RA.

Within our RA group, more physically active patients scored better in almost every domain of SF-36 than less physically active patients, and therefore patients with greater habitual physical activity levels reported feeling better than less physically active patients. This is in keeping with a previous study that showed exercise to improve the sense of well being in a

group of females with RA of a similar age range to our participants (4). These findings imply that, although not necessarily having an effect on disease activity, higher levels of habitual, ambulatory physical activity are associated with improved quality of life and sense of well being, potentially making the disease easier to cope with.

Despite our RA group not nearly meeting the current recommended guidelines for physical activity (30 minutes in moderate to vigorous activities every day of the week (19)), those that simply had higher habitual physical activity level fared better on assessments of functional status and well being despite the lack of association with disease activity. It is important to develop healthy, feasible guidelines for patients with chronic limitations of movement, potentially focusing more on increasing light activity and decreasing sedentary activity as an adjunct to increasing moderate to vigorous activity where possible. Patients with RA may need frequent rest breaks depending on their severity of their disease (5), and it might be necessary to develop different Actical cut-off points for activity levels in people with chronic pain conditions in order to allow for the increased periods of non-movement time to be considered. The Actical was able to quantify ambulatory habitual physical activity levels in this group of patients with RA, which is the first step in developing guidelines for this population.

SDAI was not significantly correlated with physical activity. We attribute the absence of a relationship between physical activity and SDAI to the fact that SDAI is comprised largely of tender and swollen joint counts, 26 out 28 of which, are upper limb joints. An activity monitor placed on the hip would measure only ambulatory, lower limb activity and not upper limb activity. It may be necessary to look at the associations between physical activity and deformity of the joints (especially lower limb joints) as assessed by an X-ray or a clinical

measure of joint deformity such as the rheumatoid arthritis articular damage score (RAAD score) (35).

The limitations of this study include the cross sectional design, which limits the causality conclusions we can draw. While increased habitual physical activity levels were associated with improved well being and better functional status, it is not clear if this is the cause or the effect. Also we focused only on females, and these results cannot necessarily be extrapolated to males, although the incidence of RA is much higher in females (26). We also excluded patients who were using assistive walking devices, which limits the extrapolations we can make to RA patients needing to make use of such devices. Lastly, we did not manage to successfully match the ages of the control group with the RA group, and although this was controlled for in the analysis, it is still a limitation to the study.

In conclusion, RA patients have decreased habitual physical activity levels in comparison to healthy, matched controls. The daily physical activity patterns of the patients with RA do not show the same bimodal peaks seen in healthy control participants and are likely to be related to periods of morning stiffness and fatigue. The activity counts recorded by the Actical accelerometer correlate well with the HAQ-DI, giving the Actical construct validity as a novel outcome measure in RA. Furthermore, patients with higher physical activity levels scored better with regards to the SF-36 in both physical and mental domains. A longitudinal study is needed to assess the responsiveness of physical activity to changes in disease activity.

Acknowledgments:

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Key Messages:

1. Actigraphy counts are negatively correlated with HAQ scores in patients with RA.
2. More physically active RA patients scored better than the less physically active patients on many components of the SF-36.
3. RA patients demonstrated quantifiable bimodal decreases in daily physical activity in the morning and late afternoon.

2.2. Study 2 – Changes in Physical Activity Measured by Accelerometry Following initiation of DMARD therapy in rheumatoid arthritis[1]

1. Prioreschi A, Hodkinson B, Tikly M, McVeigh JA. Changes in physical activity measured by accelerometry following initiation on DMARD therapy in rheumatoid arthritis. Rheumatology. 2014:53(5);923-6

Please note that the version presented in this thesis is an extended version of the published manuscript. Table and Figure numbers, as well as citations have also been modified from the published version in order to align with the numbering of the thesis.

Changes in physical activity measured by accelerometry following initiation of DMARD therapy in rheumatoid arthritis

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Word count:

1738

Key Words:

Physical activity, DMARD therapy, accelerometry, rheumatoid arthritis.

Short Title:

Objective changes in physical activity following DMARD therapy in RA

Abstract:

Introduction: This study aimed to assess changes in disease activity, as well as corresponding changes in objectively measured physical activity levels in response to commencement of DMARD therapy in drug-naïve patients with rheumatoid arthritis (RA). **Methods:** Eighteen RA patients completed this study as did 18 age, sex and body mass index matched healthy control participants. At baseline, and again after three months, Actical accelerometers were fitted on the dominant hip of each participant for two weeks; and RA patients completed disease activity and functionality questionnaires. **Results:** After three months of drug therapy, patients had significant improvements in disease activity as assessed by CDAI ($p<0.001$) and functional ability as assessed by HAQ ($p<0.001$). In parallel with these changes, the average activity counts in sedentary thresholds decreased ($p=0.010$), while average activity counts within higher intensity thresholds increased. At baseline, RA patients were less physically active than control participants in the morning ($p=0.048$), and in the late afternoon ($p=0.016$), yet these diurnal differences were no longer evident after the DMARD intervention. Multiple regression analysis showed that the change in moderate activity was associated with a decrease in C-reactive protein ($\beta=-0.922$, $p=0.026$), and the decrease in sedentary activity and increase in moderate activity were associated with decreased morning stiffness of the joints ($\beta=0.694$, $p=0.035$ and $\beta=-0.927$, $p=0.024$ respectively). **Conclusion:** DMARD therapy significantly improved disease activity in patients with RA, and these improvements were paralleled by subsequent improvements in physical activity levels. Changes in physical activity levels were significantly correlated with changes in disease activity measures.

Introduction:

Patients with rheumatoid arthritis (RA) are generally more sedentary than their healthy counterparts. RA is associated with physical disability as a consequence of a combination of active synovitis and joint deformities, as well as chronic pain (123), all of which force patients into a sedentary lifestyle. There is growing interest in the use of patient reported outcomes measures in the assessment of RA, along with standard clinical and physician assessments. Of these patient reported outcomes; physical functionality has been shown to be one of the most important outcomes, as well as the most commonly assessed outcome (33), (34). The current methods of assessing physical functionality are, however, subjective, and to date no objective measures of physical functionality for patients with RA have been routinely included in clinical practice or in clinical trials.

Accelerometry has been used previously in patients with RA with varying objectives (85), (86, 124). There is, however, still a paucity of knowledge regarding the habitual physical activity levels (this refers to activities of daily living such as locomotion, leisure activities and conscious exercising) of patients with RA, or the effects of their sedentary lifestyle on their disease activity. Although it is likely that the chronic pain patients with RA experience on a daily basis makes an active lifestyle difficult to accomplish, it is unclear whether RA patients would spontaneously become more habitually physically active if their symptoms were controlled, or whether disease activity and habitual physical activity levels are indeed associated with each other.

In our study we aimed to explore the changes that may occur in physical activity levels in patients with RA in response to commencement of drug therapy, as well as the use of accelerometry as an outcome assessment of physical functionality in RA. This was achieved

by objectively measuring habitual physical activity levels in newly diagnosed, drug-naïve patients with RA using a well validated Actical accelerometer (81), and then re-evaluating their habitual physical activity levels after three months of being treated with standard RA drug therapy. Secondly, we aimed to determine whether there were any associations between changes in disease activity levels and changes in habitual physical activity levels at the end of a three month drug intervention.

Patients and methods:

Inclusion and Exclusion Criteria:

Of the 22 patients initially enrolled in this study, 18 patients completed the study and were included in the results. The remaining four participants were lost to follow up. Patients were included if they were female, with newly diagnosed RA fulfilling the 1987 ACR criteria (114), were naïve to disease modifying anti rheumatic drug (DMARD) therapy, and if they were attending the Chris Hani Baragwanath Academic Hospital Rheumatology Clinic (South Africa). Exclusion criteria were co-morbidities that could affect physical activity such as previous history of a stroke, cardiac complications or physical disability, use of assistive walking devices, pregnancy, or patients who had been previously treated for RA. These patients were matched with 18 healthy control participants for age, sex, and body mass index (BMI) from the same geographical area. Ethical approval was obtained from the human research ethics committee of the University of the Witwatersrand (M110430 and M110236), and complied with the Declaration of Helsinki. All participants signed written informed consent, and were free to withdraw from the study at any time.

Study Design:

Patients were assessed at baseline and again after three months. Upon enrollment, patients completed various health related quality of life (HRQoL) and functionality questionnaires (as described below), and were assessed for disease activity by their physician. Anthropometric measurements were also taken. Participants were immediately fitted with an Actical accelerometer (Respironics Inc, Murrysville, USA), which was worn on a Velcro belt on the hip of the dominant leg for two consecutive weeks. Acticals were removed only when the participants were bathing/showering or participating in any other water-based activities. No medication was given for the initial two weeks following diagnosis, while the Actical was being worn with the exception of intra-articular steroid injections (methylprednisolone acetate) in severe cases and only if the affected joint was on the upper limb so as not to affect Actical readings. After the two week period, patients returned to the clinic and were started on medication as prescribed by their physician (BH) in order to achieve a low disease activity (methotrexate 15mg/week which was escalated by 5mg/week every month until low disease activity was achieved, and prednisone 7.5mg/day). This drug treatment plan was consistent between patients for the three month period. Patients then continued taking their medications for three months, where after they returned to the clinic for their follow up assessment where all measurements were repeated including wearing the Actical for two weeks. Control participants were fitted with an Actical on the dominant hip for two weeks at baseline only.

Physical Activity and Anthropometry Measurements:

Actical data were recorded in one minute epochs and data were reduced by removing only full days of non-wear time as assessed either by observation of the data where a full day of consistent zero activity counts was recorded, or as indicated by the participant if a day of wearing the Actical was missed. The remaining data are referred to as the “wear period” in a

similar manner to that described by Semanik et al in 2010 (84). Data for the wear period were divided into thresholds, namely sedentary, light, moderate or vigorous activity according to the activity counts recorded and the inbuilt algorithm calculated by the Actical software (Respironics Inc, Murrysville, USA). Activity data for the patients were represented as average activity counts during the 'awake' period (patients had an average 16.0(2.3) hour awake day at baseline and 15.7(1.3) hours at follow up, p=0.614) per hour over the two week period. These data were then expressed as average activity counts within each threshold per day as recommended by Pate et al in 2008 (4). The 95th percentile of the activity counts recorded over the period for each participant was also noted in order to eliminate any outliers in maximal activity counts. Patients were fitted with the same Actical at baseline and at the three month follow up so as to avoid any inter-device differences in recording of data. Height (to the nearest cm) and weight (to the nearest kg) were taken using a standard stadiometer and scale (Holtaine, USA), with participants barefoot and not wearing excess clothing. Equipment was routinely calibrated throughout the study.

Measures of Disease activity, Functional Disability, and HRQoL:

Disease activity was assessed using Clinical Disease Activity Index (CDAI), and was done throughout the study by the same physician (BH) (18). C-reactive protein (CRP) in mg/dL was documented, however data were missing for six patients and thus CRP data is reported for 12 patients only. RA patients were also questioned on their pain levels using a self-assessment scale where possible scores range from 0 to 5, with a score of 5 indicating unbearable pain and 0 indicating no pain, as well as on the duration of the stiffness of their joints on the morning of their assessment. Patients also completed the modified HAQ; a well validated RA specific assessment of functionality (29) where the total score ranges from the best possible result (score of 0) to the worst possible result (score of 3). Patients completed

the SF-36, a generic instrument to measure HRQoL comprising of eight categories of health (125) where a higher score indicates a better outcome.

Statistical Analysis:

Sample size calculation was based on a *Priori* power analysis (β=0.8) showed that at a 10% level, a sample size of 17 patients would be needed to detect a difference in sedentary activity with a power of 82% (126). Paired Student's t-tests were used to compare changes from baseline in continuous variables in order to assess any changes in these data over the three month period for parametric data, and Wilcoxon matched pairs tests were used for non parametric data. Unpaired students t-tests were used to compare patient and control characteristics at baseline. Spearman's correlations were run to determine any correlations between activity data and clinical data. For categorical variables, a Chi-squared contingency test and a Fishers exact test were used to determine differences in distribution of patients within categories before and after drug therapy. A backwards stepwise multiple regression was run to determine predictors of various changes in disease activity outcomes. All statistical analyses were done using STATISTICA v10.0 (Tulsa, OK) and a p-value of <0.05 was considered significant.

Results:

RA group compared to control group at baseline:

There were no significant differences at baseline between patients and controls with respect to age, (50(14) vs. 44(7) years, p=0.103), height, (1.59(0.06) vs. 1.60(0.11) m, p=0.629), weight, (76(22) vs. 73(11) kg, p=0.677) or BMI, (30(8) vs. 29(5) kg/m^2, p=0.613). The mean BMI was in the obese range in both groups according to the WHO classification criteria. The symptom duration of the RA patients at baseline was 43(55) months.

Disease activity changes in the RA group following DMARD therapy:

As shown in Table 2.3, there was a significant improvement in disease activity, HAQ scores, and in a number of domains of the SF-36 over the three month period. Similarly, height increased significantly by 1cm after three months of drug therapy. The majority of patients at baseline (78%) had severe functional disability, defined as a HAQ score ≥1.5, yet only a minority (17%) remained in this category at follow up ($p<0.001$). Furthermore, morning stiffness improved significantly over the three month period, from 101(64) to 46(56) minutes at follow up ($p=0.048$). Patient pain scores also improved over the three month period from 2.6(0.8) to 1.5(0.8) ($p<0.001$). Clinical disease activity index decreased significantly, as can be seen in Table 2.3, as did each individual component of CDAI: namely tender joint count (11(6) to 3(4), $p<0.0001$), swollen joint count (9(6) to 2(3), $p<0.0001$), physician global assessment (7(3) to 3(2) out of 10, $p=0.003$) and patient global assessment (8(3) to 4(2) out of 10, $p=0.003$). The percentage of participants in each category of CDAI: namely remission (≤2.8), low disease activity (≤10), moderate disease activity (≤22), and severe disease activity (>22); was significantly improved following the three month drug intervention ($X^2=21.57$, $p<0.0001$) as can be seen in Table 2.3.

Table 2.3. RA patient characteristics of demographic and clinical features at baseline and three months after commencing drug therapy.

	Baseline (n=18) Mean(SD)	**Follow up (n=18) Mean(SD)**	**p-value**
Height (m)	1.59(0.06)	1.60(0.06)	0.021 *
Body mass (kg)	76(22)	76(21)	0.171
BMI (kg/m^2)	30(8)	30(7)	0.850
CDAI	41(11)	14(8)	<0.001 *
Remission	1	3	
Low Disease Activity	0	3	
Moderate Disease Activity	2	10	
Severe Disease Activity	15	2	
HAQ (/3)	1.94(0.87)	0.98(0.76)	<0.001 *
C-reactive protein (mg/dL) #	32.59(35.84)	23.90(38.04)	0.060
SF-36			
Physical Function	41(25)	49(26)	0.252
Role Physical	10(17)	28(39)	0.061
Body Pain	26(21)	48(17)	<0.001 *
General Health	53(19)	54(29)	0.868
Vitality	38(14)	55(22)	0.002 *
Social Functioning	55(21)	60(24)	0.488
Role Emotional	22(38)	50(45)	0.047 *
Mental Health	60(18)	63(16)	0.470
Composite Physical Health	34(14)	47(19)	0.003 *
Composite Mental Health	46(15)	56(20)	0.038 *

* $p<0.05$
# CRP values (n=12)
BMI: Body mass index; CDAI: Compound Disease Activity Index; HAQ-DI: Health Assessment Questionnaire Index; SF-36: Short Form-36.

Physical activity changes in the RA group following DMARD therapy:

Table 2.4 shows the baseline and follow up data of the accelerometry measures. At the three month follow up there were significant decreases in sedentary activity measures, and significant increases in light activity measures compared to baseline. The average activity counts in sedentary activity at the follow up decreased significantly from baseline, and the same was true for the activity counts at the 95th percentile within sedentary activities. A trend was seen for increased average activity counts in light activity at the follow up from baseline, while the activity counts in the 95th percentile of light activity increased significantly. There were no significant changes measured in moderate or vigorous activity thresholds.

Table 2.4. Physical activity measures at baseline and at the three month follow up in the RA group

	Baseline (n=18) Mean(SD)	Follow up (n=18) Mean(SD)	p-value
Average activity (counts/day)	110908(42942)	112502(61190)	0.286
Sedentary activity			
Average counts	428(124)	354(158)	0.012 *
95th percentile counts	995(283)	837(253)	0.004 *
Light activity			
Average counts	1208(665)	1496(810)	0.094
95th percentile counts	3461(1453)	4451(2057)	0.039 *
Moderate activity			
Average counts	5431(3062)	5615(4266)	0.983
95th percentile counts	22087(12292)	24271(16074)	0.948
Vigorous activity			
Average counts	50(135)	44(120)	0.612

* Activity data significantly improved at follow up as compared to baseline ($p<0.05$)

We further divided the activity counts into three hourly intervals throughout the day as shown in Figure 2.5. We compared these data to those obtained from a control group of healthy participants. Although there were no significant differences between the average activity counts spent in each time period at baseline and at the three month follow up within the RA group; at baseline the RA patients were significantly less active than the matched control group in the morning ($p=0.048$) and the late afternoon ($p=0.016$). Importantly, at the three month follow up, these differences were no longer evident between the RA patients and the control group in the morning ($p=0.624$) or the late afternoon ($p=0.402$), or at any other time interval.

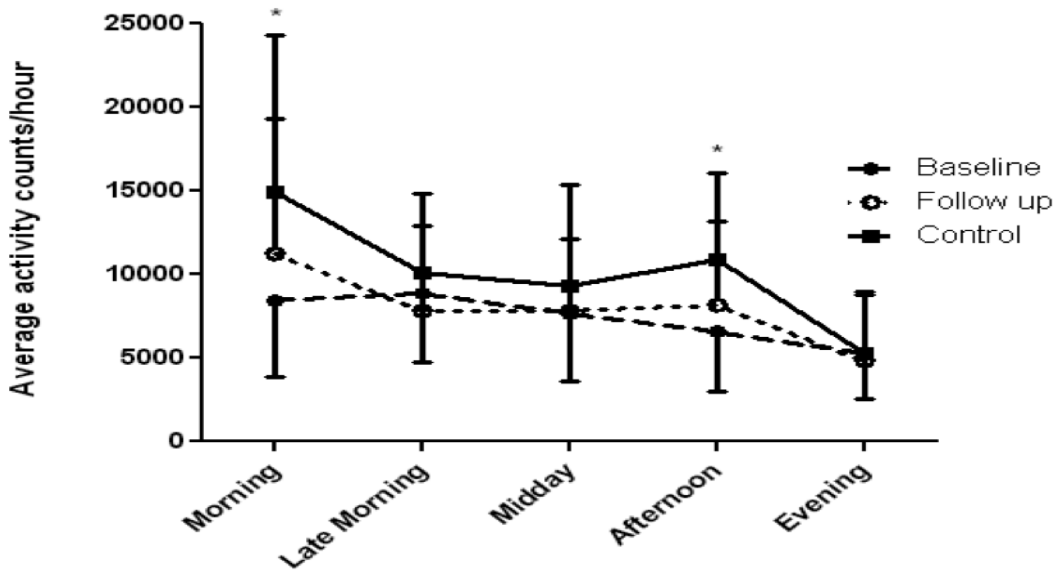


Figure 2.5. Average activity counts spent in three hourly time intervals throughout the day at baseline (solid circle) and again at the three month follow up visit (clear circle). Data are also compared with the control group (solid square).
* $p<0.05$ between the patients at baseline and the control group.

Multiple regression analysis:

The change from baseline in the patient's disease activity measures (CDAI, HAQ, CRP, SF-36 components, morning stiffness and patient's pain assessment) and the change from baseline in their activity data (95^{th} percentile of activity counts in each threshold) were correlated using Spearman's correlations. Change in vitality score was positively correlated with change in average daily activity count (R=0.646, p=0.005), change in HAQ was negatively correlated with change in vigorous activity (R=-0.536, p=0.022), and change in CRP was negatively correlated with change in moderate activity (R=-0.577, p=0.039). Furthermore, since height changed significantly from baseline, change in height was also correlated with the change in all disease activity and physical activity measures and was found to be significantly positively correlated with change in tender knee joint count (R=0.528, p=0.043). Change in height was not correlated with any other variables. Significant correlations were then entered into a multiple regression analysis and the results are shown in Table 2.5.

Table 2.5. Multiple regression analysis showing change in disease activity indices vs. change in physical activity data.

Independent variable (change from baseline)	**Predictor variable** (change from baseline)	**β value**	***p*-value**
Morning stiffness	Sedentary activity	0.694	0.035
	Moderate activity	-0.927	0.024
CRP[#]	Moderate activity	-0.922	0.026

[#] CRP values (n=12)
C-reactive protein (CRP).
All represented correlations were significant; regression was run as a backward step-wise analysis.

Discussion:

In this study we report novel data on objectively measured habitual physical activity levels in patients with RA before and after starting DMARD therapy. Following three months of DMARD therapy there was a significant improvement in disease activity, functional ability and HRQOL as measured by CDAI, HAQ, and the SF-36 respectively. Patients reported having less pain after three months of drug therapy, which was likely a contributing factor to their improved physical activity levels, along with their significantly lower tender and swollen joint counts as assessed by their physician.

In parallel with these improvements, objective measures of habitual physical activity also improved significantly. Following the DMARD therapy intervention there was a significant reallocation of activity counts from participation in sedentary activity (activities requiring minimal energy expenditure over and above resting metabolic rate such as lying down and sitting) to increased participation in light activity (activities such as standing up and light walking) of activity. The decreased mean activity counts in the sedentary activity threshold in

conjunction with the increased mean activity counts within the light activity threshold, is indicative of patients breaking up their sedentary activities with light activities more frequently than before the DMARD therapy intervention. These observed increases in habitual physical activity show the effectiveness of the Actical accelerometer in measuring the response of physical activity to change in disease activity.

We also assessed the average activity counts in three hourly intervals throughout the day in order to observe daily fluctuations in habitual daily activity levels. Compared to control participants at baseline, RA patients had significantly lower activity levels in the morning and in the late afternoon. These differences were no longer evident after the DMARD therapy intervention. The lower activity levels observed at baseline in the early morning and late afternoon are likely to be related to two common symptoms of RA, namely early morning stiffness and late afternoon fatigue. After the DMARD therapy intervention, the length of morning stiffness time was significantly shorter, and this change was significantly associated with an increase in moderate activity counts. Although we did not assess afternoon fatigue levels subjectively, the vitality component of the SF-36 has been shown to be a relevant measure of overall fatigue in RA (127), and these scores increased significantly over the three month period. Furthermore, this improvement in vitality score was positively associated with the increase in average activity counts measured. Our results indicate that the drug therapy attenuated differences in habitual physical activity levels between healthy control participants and RA. In our study, DMARD therapy improved the common symptoms of RA over three months, and the Actical accelerometer was sensitive enough to detect changes in habitual physical activity in response to drug therapy.

Apart from a decrease in disease activity and a concurrent increase in habitual physical activity levels in our patients, there were also strong associations between these outcomes measures. All of these correlations indicated that improvements in disease activity were associated either with increased physical activity (at either light, moderate or vigorous intensities), or with decreased sedentary activity. The Actical data were significantly correlated with every one of the well-validated, standard outcome measures of RA that were assessed in this study.

An unexpected finding was the significant increase in height observed in our patients (by 1cm), after three months of DMARD therapy. Possibly, the significant positive correlation between change in tender knee joint count and change in height could account for this. It is likely that the increase in height is due to a minor flexion deformity of the knee that improved following DMARD therapy, allowing patients to stand more upright. The fact that we did not measure flexion angles limits the conclusions we can draw from this finding. Patients also reported being in significantly less overall pain after three months, which could further explain their ability to stand taller. An alternative explanation to the increase in height could be related to bone loss associated with RA (128). Improved bone status (after a whole body vibration intervention) in cyclists with low bone mass has been shown to be associated with an increase in height (129). Although this result should be interpreted with caution, stature is an important variable to monitor in patients with low bone mass (130). Decreases in height are observed with worsening bone loss, as well as with aging, due to narrowing of intervertebral disks and loss of vertebral height (131). An increase in height, such as those seen in our RA patients after three months of DMARD therapy, could be also be indicative of improvements in bone health due to the improvements in disease activity, although we did not measure bone mineral density in this study.

The placement of the Actical on the hip only can be considered a limitation of our study. The hip placement means that only lower limb movement could be measured. The exclusion of male participants (although the majority of patients with RA are female (118)), as well as the fact that the participants in this study were obese means that our results cannot necessarily be extrapolated to male RA patients and those within the normal BMI range. The exclusion of patients using assistive walking devices further limits the conclusions we can draw with regards to patients who are more severely disabled. Future studies should aim to build on the novel work presented here, by using study designs with larger sample numbers and a longer duration of study, or by including some form of activity intervention in these patients and monitoring changes in disease activity.

Conclusion:

The results of this study indicate that patients treated with DMARD therapy became less sedentary and started undertaking more light physical activity, and following patterns of daily activity levels similar to those of healthy individuals. Changes in disease activity were correlated with changes in physical activity, further clarifying the associations between disease activity and physical activity levels in RA. The results of this study also present accelerometry as a tool for assessing changes in physical activity in response to DMARD therapy, and support the use of accelerometry as a concurrent measure of disease activity and physical function in patients with RA.

Key Messages:

1. Objectively measured physical activity levels improve in response to DMARD therapy in patients with RA.
2. Following DMARD therapy, patients start to undertake less sedentary, and more light activity.
3. Daily patterns of physical activity start to resemble those of a healthy population following DMARD therapy.
4. Improvements in physical activity levels are correlated with improvements in disease activity.

Conflict of interest:

The authors state that they have no conflicts of interest to declare

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2.3. Study 3 (Baseline) – Higher Habitual Activity Levels Are Protective of Bone Mass in Patients with Rheumatoid Arthritis[1]

1. Prioreschi A, Makda MA, Tikly M, McVeigh JA. Under review at BMC Musculoskeletal Disorders

Please note that Table and Figure numbers, as well as citations have been modified from the submitted version in order to align with the numbering of the thesis.

Higher habitual physical activity levels are protective of bone mass in patients with rheumatoid arthritis

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Keywords:

Rheumatoid arthritis, physical activity, accelerometry, osteoporosis

Abstract:

Background: Prolonged periods of time spent in sedentary behaviour by patients with rheumatoid arthritis (RA) may increase the likelihood of the development of osteoporosis. We aimed to determine the associations between habitual physical activity levels and bone health in patients with RA. **Methods:** Twenty nine female patients with RA, recruited from Soweto, South Africa, were assessed for site-specific bone mineral density (BMD) using dual x-ray absorptiometry (DXA), and were classified as having low or normal bone mass according to peak reference values at the hip. Habitual physical activity levels were measured objectively using an Actical accelerometer over a two-week period. Patients were assessed for RA disease activity using the Compound Disease Activity Index (CDAI), and functional disability using the Health Assessment Questionnaire (HAQ). **Results:** Twenty-one patients were classified as having normal bone mass, and eight had low bone mass. There was no difference in the age of the two groups of patients (51(8) in the normal bone mass group vs. 57(12) years in the low bone mass group, p=0.19). Patients with normal bone mass reported less functional disability (0.96(0.71) vs. 1.57(0.74), p=0.05), and had a trend towards lower RA disease activity than patients with low bone mass (7.7(6.1) vs. 13.8(10.8), p=0.07). Further, habitual physical activity levels were greater in the normal bone mass group (p<0.01). Patients with normal bone mass spent on average two hours less per day in sedentary activity (65(4)% vs. 73(2)%, p<0.01), over 70 minutes more time in light activity (23(1)% vs. 18(2)%, p<0.01), and over 50 minutes more in moderate activity per day (12(3)% vs. 8(2)%, p<0.01) than did patients with low bone mass. Patients with normal bone mass also broke up their sedentary time more frequently per day than those with normal bone mass (72(21) vs. 53(18) times per day, p=0.03), and those patients who met the recommended physical activity guidelines for a rheumatic population had significantly lower Z scores than patients who did not meet the guidelines (p=0.03). **Conclusions:** The results of

this study indicate that higher habitual activity levels may be protective of bone health in patients with RA, and should be encouraged as an affordable, sustainable therapeutic option.

Introduction:

Rheumatoid arthritis (RA) (the most common autoimmune condition), results in systemic and local inflammation, disability, joint erosion and musculoskeletal deterioration. Osteoporosis, -a skeletal disease resulting in low bone mass (46) which manifests clinically as fractures (132), is a major source of morbidity for people with RA (133). The presence of circulating inflammatory cytokines, decreased mobility of patients with RA (resulting in a sedentary lifestyle), as well as certain medications taken to treat the disease such as corticosteroids and methotrexate, all contribute towards an increased incidence of osteoporosis in patients with RA (50). The incidence of osteoporosis in patients with RA has been reported to be almost double (18%) of that in non-RA patients (10%) (134-136).

Studies have shown that the majority of bone density loss in RA occurs in the first six months of acquiring disease (47). Furthermore, patients with higher disease activity have been shown to exhibit greater loss in bone mineral density (BMD), as well as higher indices of bone metabolism (137). One third of women with osteoporosis will incur a fracture in their lifetime (138); and the decreased muscle mass present (sarcopenia) in patients with RA predisposes these patients to falling, further increasing fracture risk (139). Patients with RA often present with sarcopenia and either preserved, or increased fat mass (sarcopenic obesity) (63).

Physical activity is an important, non-pharmacological method to increase (or preserve) BMD (140), and the most efficient means to increase lean muscle mass and therefore reduce sarcopenia in RA (61). Furthermore, it is an inexpensive treatment option. Numerous exercise

interventions have been implemented in healthy participants with low BMD with successful results (140), however fewer studies exist examining the effects of exercise on BMD in patients with RA. Haakkinnen et al in 2001 reported that low intensity strength training over a period of two years in a group of RA patients increased BMD significantly more so than stretching exercises did in a control group of RA patients (who experienced a decreased BMD) (141).

To the best of our knowledge, the association between objectively measured habitual physical activity levels and BMD in patients with RA has not been studied. Kroot et al (2001), found that BMD loss was significantly attenuated in postmenopausal RA patients who had a higher activity load (as assessed by a questionnaire that quantified time spent walking and multiplied it by body mass in order to obtain 'activity load' at the hip), than those with a lower activity load, and experienced a greater loss in BMD over a six year period (142).

Other cross sectional studies report lower levels of subjectively measured physical activity to be correlated with lower BMD values in patients with RA (48); and although these studies are important, there is still a lack of evidence linking objectively measured habitual physical activity levels to bone status in patients with RA. We have recently used accelerometry as a means to quantify habitual activity levels in patients with RA (143). The current study aimed to determine the association between objectively measured habitual physical activity levels (using an Actical accelerometer) and bone health in a group of patients with RA.

Methods:

Participants and Study Design:

Thirty one Black, female patients with established RA participated in this study. Patients were recruited from the Rheumatology Clinic at the Chris Hani Baragwanath Academic

Hospital, Soweto, South Africa between April 2013 and September 2013. Consenting patients were included if they were older than 18 years, had been diagnosed with RA (according to the 1987 ACR criteria (123)) at least three years previously, were on stable drug therapy (prednisone <10mg/day), and had been for at least three months previously. Patients were excluded if they were HIV+, were using bisphosphonates or corticosteroid injections, had any co-morbidities that could potentially impact on physical activity levels, were using assistive walking devices, had previously had hip or knee joint replacement surgery, and if they were pregnant. Ethical approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (M130113), and all participating patients gave written informed consent.

All patients were assessed at two separate visits. At the first visit patients were assessed for disease activity using the Compound Disease Activity Index (CDAI) by the same physician, and were asked to complete the modified Health Assessment Questionnaire (mHAQ), the Short Form-36 questionnaire (SF-36), as well as a demographics questionnaire. At the second visit, patients underwent a Dual X-Ray Absorptiometry (DXA) scan to assess Bone Mineral Density (BMD) and body composition. Anthropometric measurements were taken and included height (measured to the nearest mm using a stadiometer (Holtaine, UK)), and body mass (measured to the nearest 100g using a standard digital scale (Dismed, USA), as well as waist and hip circumference, and leg girth (measured to the nearest cm using a standard tape measure). From these measurements Body Mass Index (BMI) was calculated, as was waist:hip ratio.

Physical Activity:

Patients were fitted with an Actical (Respironics Inc., Murrysville, PA, USA) accelerometer (for the assessment of habitual physical activity) that was worn on a Velcro belt on the hip of the dominant leg for a two week period. Patients were instructed to wear the accelerometer all day, and to remove the device only while sleeping, bathing or showering. Patients then returned the accelerometer to the clinic two weeks later. Actical data were recorded in one minute epochs and data were reduced by removing only full days of non-wear time as observed by a full day of zero activity counts. Sleep time was removed by direct observation of the data, and only the remaining data were considered as wear time.

Data Reduction:

Data were reduced according to standard criteria (25) where non-wear time was considered as more than 60 minutes of consecutive zero activity counts. A valid day was considered to have at least 10 hours wear time. Non-valid days were removed, and patients were excluded if they had less than four valid days of data. Two patients were consequently excluded, and data analysis was conducted on the remaining 29 patients.

Activity Data:

The Actical accelerometer records activity counts, which (based on the number of counts per epoch), are then classified by the inbuilt Actical software into thresholds of intensity; namely sedentary (0-100 counts), light activity (100-1485 counts), moderate activity (1486-5557 counts), and vigorous activity (≥5558 counts). Data were thus considered "active" data if a minute epoch had an activity count that was greater than 100 (i.e.: light to moderate/vigorous activity). Activity bouts were then calculated as the number of times per day that at least 10 consecutive minutes of "active data" were recorded. We defined compliance with physical activity guidelines as ≥30 min of "active" time performed in bouts of 10 minutes at least

three times per week according to guidelines for rheumatic and healthy populations (4, 88). The number of times that sedentary activity was "broken up" was calculated as the number of times per day that a sedentary minute epoch (<100 counts) was followed by an active minute epoch (>100 counts); and these data were thus considered as a break in sedentary time (144). Data were thus reported as average activity counts per day; percentage of time spent in sedentary, light, moderate and vigorous activity thresholds; average number of activity bouts per day, as well as average number of sedentary breaks per day.

BMD assessment:

All patients were assessed for site specific areal BMD at the left hip, lumbar spine (L1-L4), and whole body. All scans were performed by the same qualified technician on the same machine (Hologic QDR 4500A, Hologic, Boston, USA). The machine was routinely calibrated throughout the study, and a phantom spine was scanned daily to determine coefficients of variation of the machine. Coefficients of variation during the course of the study for spine BMD were 0.31%.

In order to classify patients' bone status, T and Z scores were calculated based on the total hip BMD, and according to the reference values in the NHANES database (145). T scores were calculated using reference values for Caucasian women at peak bone mass (BMD=0.971 with a SD of 0.114), and Z scores were calculated using reference values for age, sex and ethnicity- matched women. According to the WHO classification criteria, a T score >-1 SD above the mean reference value is considered normal, while a T score ≤-1 SD and >-2.5 SD the reference value is considered osteopaenic (low bone mass), and a T score ≤-2.5 SD the reference value is considered osteoporotic. Therefore, in the current study, we

classified patients with a T score ≤-1 at the hip into a low bone mass group and those with a T score>-1 into a normal bone mass group.

Total lean body mass (LBM) was obtained from the body composition component of the whole body DXA scan, and appendicular lean mass (ALM) was calculated by adding left and right- arm and leg- lean masses. Thereafter, linear regression was used to model the relationship between ALM on height and fat mass. Residuals of the regression were used to identify those with lower ALM than predicted for their fat mass. Participants with a negative residual value were considered relatively sarcopenic, and those with a positive residual value were considered as relatively muscular. The equation was as follows:

ALM=-14.69+(0.25*percentage fat mass)+(16.08*height)

Sarcopenia was set at the 20^{th}%ile of the distribution of the residuals as suggested by Newman et al in 2003 and Figueirdo et al in 2014 (146-147).

Statistical Analysis:

Statistical analysis was carried out using Statistica version 12. All data are presented as mean(SD) (except where otherwise stated), and a p value ≤0.05 was considered significant. Student's unpaired t-tests and Mann Whitney U tests were used to compare physical activity, patient characteristics, and RA disease activity data between low and normal bone mass groups. A Fishers exact test was used to determine differences in prevalence of sarcopenia between groups. Pearson's correlation was used to determine associations between known confounders of BMD in patients with RA. Thereafter, an ANCOVA was used to assess differences in physical activity patterns between the low and normal bone mass groups. The strongest univariate correlates of total hip BMD, that were also found to be different between the two groups (excluding collinear variables), were used as covariates i.e.: disease duration,

body mass, height and mHAQ. Power analysis indicated a 99% chance of detecting a difference between the two groups in average activity counts per day as significant at the 5% level (two tail).

Results:

Thirty one patients with established RA completed this study. Two patients were excluded from the analysis due to invalid activity data. Of the remaining patients, eight were classified as having low bone mass according to peak BMD reference values at the total hip, and the remaining 21 were considered to have normal bone mass. Patient characteristics are shown in Table 2.6. There was no significant difference in age between the two groups, however RA disease duration was almost twice as high in the low bone mass group (although not significant). Patients with low bone mass also had a lower BMI ($p=0.03$), as well as smaller waist and hip circumferences ($p=0.01$ and $p=0.02$ respectively), and a trend towards lower leg girth ($p=0.06$). Waist:hip ratio was, however, not significantly different between the two groups (0.83(0.06) vs. 0.80(0.05), for the normal bone mass and low bone mass groups respectively, $p=0.25$). Furthermore, patients with low bone mass had significantly less body fat ($p=0.02$), and significantly lower ALM ($p<0.01$).

Table 2.6. Participant characteristics of low and normal bone mass groups. Data are mean(SD).

	Normal Bone Mass (n=21)	Low Bone Mass (n=8)	p-value
Age (years)	51(10)	57(12)	0.19
Disease Duration (years)	9.6(8.5)	16.5(10.6)	0.08
Height (m)	1.59(0.07)	1.52(0.07)	0.03*
Body mass (kg)	88.85(21.30)	63.51(11.57)	<0.01*
BMI (kg/m^2)	35.30(7.63)	28.20(7.82)	0.03*
Waist circumference (cm)	101.19(15.25)	85.00(10.46)	0.01*
Hip circumference (cm)	122.21(16.65)	106.06(11.79)	0.02*
Leg girth (cm)	64.86(8.98)	57.50(8.62)	0.06
Fat mass (kg)	37.18(11.87)	24.90(9.59)	0.02*
ALM (kg)	20.29(3.69)	15.47(1.95)	<0.01*
LBM(kg)	44.20(12.42)	36.18(2.83)	0.09
Sarcopenic (%)	14	25	0.59
Negative residual value (%)	57	63	0.23

*p≤0.05
BMI – body mass index, ALM – appendicular lean mass, LBM – total lean body mass.

Rheumatoid arthritis disease activity was more severe in the low bone mass group (Table 2.7). Disability as assessed by the mHAQ, was higher in patients with low bone mass (p=0.05). Tender 3(3) vs. (1(1), p=0.03) and swollen 4(4) vs. (2(2), p=0.05) joint counts were significantly higher in the low bone mass group than in the normal bone mass group respectively. Similarly, CDAI was worse (approaching significance) in the low bone mass group (p=0.07). Pain levels, duration of morning stiffness, and fatigue levels were not different between the two groups (p>0.05).

Table 2.7. Disease activity data for low and normal bone mass groups. Data are mean(SD).

	Normal Bone Mass (n=21)	Low Bone Mass (n=8)	p-value
mHAQ (/3)	1.0(0.7)	1.6(0.7)	0.05*
CDAI	7.7(6.1)	13.8(10.9)	0.07
Pain (/5)	4.2(2.6)	2.8(2.5)	0.22
Stiffness (minutes)	22(45)	31(61)	0.68
Fatigue (/5)	3.4(2.7)	4.7(3.1)	0.28

mHAQ – modified health assessment questionnaire, CDAI – Compound disease activity index.

Anthropometric and disease activity variables that have previously been shown to confound BMD in patients with RA (148) were correlated with total hip BMD. Total hip BMD was positively associated with ALM ($p<0.01$, $r=0.79$), height ($p=0.01$, $r=0.49$), body mass ($p<0.01$, $r=0.74$), waist and hip circumference ($p<0.01$, $r=0.66$ and $p<0.01$, $r=0.60$ respectively), and leg girth ($p=0.01$, $r=0.48$). Total hip BMD was negatively associated with disease duration ($p=0.05$, $r=-0.38$) and HAQ-DI ($p<0.01$, $r=-0.55$). Trends towards significant correlations were seen for age ($p=0.07$, $r=-0.34$), and CDAI ($p=0.09$, $r=-0.33$).

By study design hip BMD was significantly lower in the low bone mass group ($0.75(0.07)g/cm^2$) than the normal bone mass group ($1.06(0.11)g/cm^2$), $p<0.01$. In conjunction with having lower hip BMD, lumbar spine ($0.72(0.07)g/cm^2$ vs. $0.98(0.11)g/cm^2$, $p<0.01$) and whole body BMD ($0.93(0.06)g/cm^2$ vs. $1.12(0.08)g/cm^2$, $p<0.01$) were also lower in the low bone mass group compared to the normal bone mass group. There was no significant difference in number of days that the participants wore the accelerometers for ($p=0.60$), (Table 2.8). Patients with low bone mass also had significantly fewer breaks in sedentary activity per day than the normal bone mass group ($p=0.03$), however did not exhibit less activity bouts per day than the normal bone mass group ($p=0.36$), (Table 2.8). Participants who achieved the recommended physical activity guidelines had significantly lower hip Z scores than patients who did not meet the guidelines for physical activity, ($p=0.03$), while hip T scores were not different between those who met the guidelines for physical activity and those who did not ($p=0.12$) (Figure 2.6). Furthermore, even after adjusting for RA disease duration, body mass, height and mHAQ; physical activity indices were significantly lower in the low bone mass group than the normal bone mass group. Figure 2.7 shows the significant differences between the two groups in adjusted percentage of time spent in sedentary ($p<0.01$), light ($p<0.01$), and moderate ($p<0.01$) thresholds of activity

per day. Furthermore, the low bone mass group had fewer average activity counts per day (5425(1222)), than did the normal bone mass group (8123(2164)), p<0.01).

Table 2.8. Physical activity data and sedentary behaviour of the normal and the low bone mass group. Data are mean(SD).

	Normal Bone mass (n=21)	Low bone mass (n=8)	P-Value
Days worn	7(2)	7(3)	0.60
Weartime (hours/day)	17(3)	16(3)	0.55
Sedentary activity (min/hour)	39(6)	44(6)	0.05*
Light activity (min/hour)	14(4)	11(5)	0.09
Moderate activity (min/hour)	7(3)	5(2)	0.05*
Vigorous activity (min/hour)	0(0)	0(0)	0.40
Activity Bouts (number/day)	3(2)	2(1)	0.36
Bout time (min/bout)	13(7)	13(6)	0.96
Sedentary for 60 min (number/day)	7(3)	8(3)	0.55
Sedentary Breaks (number/day)	72(21)	53(18)	0.03*
Sedentary %	65(11)	74(10)	0.05*
Light %	23(6)	18(8)	0.10
Moderate %	12(6)	8(3)	0.06
Vigorous %	0(0)	0(0)	0.40

*p≤0.05

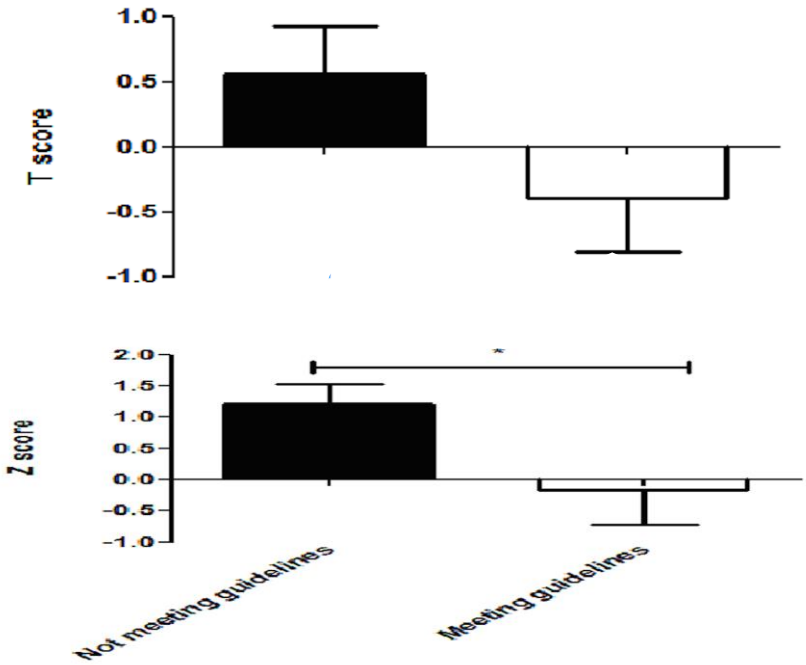


Figure 2.6. T and Z scores between patients who met the guidelines for physical activity and those who did not. *p<0.05

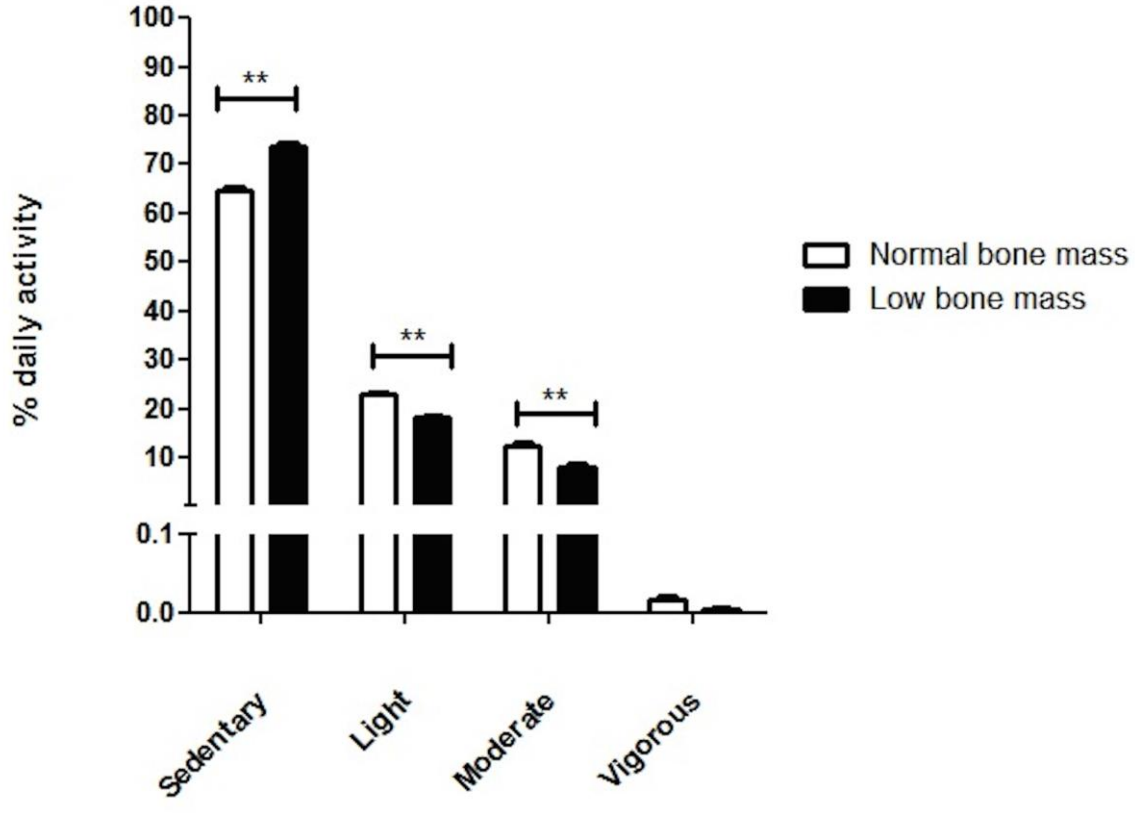


Figure 2.7. Percentage of day spent in each threshold of activity between the normal bone mass and low bone mass groups. Data are adjusted for body mass, height, disease duration and modified health assessment questionnaire (mHAQ). Data are mean(SEM)
** p≤0.01

Discussion:

We explored the association between varying habitual physical activity levels on bone health in a group of patients with RA. Patients who were classified as having low bone mass had significantly lower levels of habitual activity throughout the day than those who had normal bone mass, even after adjustment for RA disease duration and disease activity. Furthermore, patients with low bone mass spent significantly more time being sedentary, and less time in light, moderate, and vigorous activity, and had fewer breaks in sedentary time than those with normal bone mass. Our findings lend support to the possibility that higher levels of habitual

physical activity (even in a population that remains highly sedentary), and more frequent breaks in sedentary activity are associated with higher BMD in patients with RA.

In the present study, we found significant differences between the two groups for time spent in each threshold of physical activity (sedentary, light, moderate and vigorous). The greatest differences were evident in time spent in sedentary and light activity. Recently, literature has focussed on the effects of a sedentary lifestyle on metabolic health, and studies have shown that breaking up sedentary time with light activities more frequently during the day can have protective effects on metabolic health, regardless of time spent in moderate and vigorous activity (117). In our study, participants with low bone mass spent over two hours more per day being sedentary than the normal bone mass group. Our normal bone mass group spent over an hour more per day in light activity, and just under an hour more in moderate activity compared to the low bone mass group. Furthermore, the normal bone mass group broke up their sedentary time approximately 30% more frequently than did the low bone mass group, even though their cumulative sedentary time was lower. The evidence of greater amounts of time spent engaging in light and moderate physical activity in our normal bone mass group may indicate that increased physical activity, even if only to break up sedentary time more frequently, does offer some protection against RA related bone loss. These findings are important for patients with RA who have been shown to be more sedentary than their healthy counterparts (143).

In our study, participants with normal bone mass had on average 150% greater physical activity counts per day than the low bone mass group. This disparity in activity between the two groups was independent of RA disease activity or disease duration, and suggests that even low levels of habitual physical activity levels in a very sedentary population may have a

significant impact on BMD. Results from studies conducted in healthy, postmenopausal women, show that women who perform two hours more moderate activity per week than their less active counterparts have significantly higher BMD at the hip (138). Hagberg and colleagues (2001) reported that increased physical activity levels (as assessed via questionnaire) in postmenopausal Caucasian women were associated with increased BMD at the trochanter, lumbar spine, and total body (149). Of interest, the authors found that women who had been moderately active throughout their lives had higher BMD than those who had been sedentary, or even very athletic. These findings mirror the present findings, in that simply being active (whether through engaging in light or moderate activity), may be protective of bone health; and that vigorous activity (which is likely to be unfeasible in an RA population) may not be the only necessary intensity of activity for maintaining BMD. Furthermore, compared to the normal bone mass group, patients with low bone mass had significantly lower total ALM, and a trend towards lower LBM; indicating a greater presence of sarcopenia in this group. The combination of sarcopenia and low bone mass increases the likelihood of incurring a fracture through increased susceptibility to falling. Physical activity has been recommended as a means to treat both sarcopenia (61), and osteoporosis (139) in RA. Excessive time spent in sedentary activity, however, appears to be detrimental to bone health and should be counteracted as much as possible.

Guidelines for physical activity in a rheumatic population are varied in the current literature. The American College of Sports Medicine (ACSM) recommends that older adults, and people with clinically significant chronic conditions such as RA, follow similar, yet modified guidelines to those for a healthy population (30 minutes of moderate activity on most days of the week) (88). Patients with arthritis are specifically recommended to participate in low intensity activity (light to moderate), three to five times per week (150-151). Guidelines for a

healthy population recommend that periods of physical activity occur in bouts of at least 10 continuous minutes each (4). In the present study, we defined the guidelines as spending ≥30 minutes of activity accumulated in 10 minute bouts, at least three times per week. We found that those patients who met these guidelines had significantly lower Z scores than those who did not, yet T scores were not different between the two groups of patients. This is suggestive of increased levels of habitual physical activity being beneficial in attenuating loss in BMD not related to the normal aging process (i.e.: presumably related to the RA disease process) in patients with RA. Therefore, physical activity may be able to counteract disease related bone loss in patients with RA to a certain degree.

In our study, participants with normal bone mass had an average BMI which classified them as severely obese (according to the WHO), and had significantly higher fat mass than the low bone mass group. Fat mass may offer a protective role for the maintenance of bone density; and women (whether healthy or diseased) with smaller stature and lower body mass have continuously been shown to be more predisposed to developing osteoporosis (152). It is interesting to note that in the present cohort, even patients with low bone mass had an average BMI which classified them as overweight; and lower physical activity levels were related to lower bone mass even in these obese patients. In healthy, postmenopausal female populations, physical inactivity has been associated with increased risk of hip fracture in every category of BMI (153).

Low BMD has been also associated with more severe RA disease activity (48), and the present study corroborated these results. In our study, participants with low bone mass showed a trend towards higher CDAI scores, and had significantly more tender and swollen joints. Furthermore, participants with low bone mass exhibited higher mHAQ scores,

indicating a greater degree of functional impairment. Previous research has shown that greater functional impairment is associated with a greater risk of developing osteoporosis, specifically at the hip (47).

Our study is limited by a small sample size, leading to small numbers in the low bone mass group. Furthermore, discord between classification criteria for defining osteoporosis must be considered. Although the most current WHO criteria (46), and the 2013 ISCD guidelines for classifying osteoporosis state that peak normative values for a Caucasian female should be used in all female cases regardless of race; it is still unknown whether fracture risk is the same in Black and Caucasian populations (133). Another limitation is the potential confounding effect of menopausal status on bone health, which was not assessed in this study.

Notwithstanding the limitations of this study, we have used an objective measure of physical activity to show that increased habitual physical activity levels are associated with better bone mass in Black, female patients with RA, regardless of disease duration or severity. The results of the present study suggest that patients with RA should be encouraged to increase physical activity levels, and to avoid sedentary behaviour. Patients with normal bone mass were less sedentary, and engaged habitually in greater amounts of light and moderate activities, and patients who met recommended physical activity guidelines exhibited better BMD for their age. Physical activity is an important, non-pharmacological treatment for low BMD, and should be emphasised as an affordable, sustainable treatment option for patients with RA.

Competing Interests:

The authors declare that they have no competing interests.

Author Contributions:

AP conceived the study, collected all data, drafted the manuscript and analysed the data. MAM was the primary physician involved in assessing all patients. MT was involved in conceptualisation of the study design. JAM was involved in conceptualisation of the study as well as analysis of the data. All authors read and approved the final manuscript.

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2.4. Study 3 – Positive Effects of a 12 week WBV Intervention on Bone Mineral Density and Fatigue are Sustained in a Population with Established RA[1]

Trial Number: PACTR201405000823418 (19/05/2014)

1. Prioreschi A, Makda MA, Tikly M, McVeigh JA. Submitted to International Journal of Bone and Mineral Research.

Please note that Table and Figure numbers, as well as citations have been modified from the submitted version in order to align with the numbering of the thesis.

Positive effects of a 12 week WBV intervention on functional ability, bone mineral density and fatigue are sustained in a population with established RA

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Abstract

Introduction: Rheumatoid arthritis (RA) predisposes patients to developing osteoporosis. We aimed to determine the effects of a whole body vibration (WBV) intervention on functional ability, and bone mineral density (BMD), as well as on RA disease activity, health related quality of life (HRQoL) and habitual physical activity profiles in participants with stable, established RA. **Methods:** Thirty one female participants with RA were randomly assigned to a control group (CON, n=15) or a WBV group (n=16). The CON group continued with their normal activities for three months, while the WBV group underwent a three month WBV intervention, consisting of 15 minutes of intermittent vibration, performed twice per week. Participants were assessed at baseline, as well as following the intervention period, and three months post intervention for functional ability using mHAQ; for BMD and body composition using DXA; for RA disease activity using CDAI and for physical activity profiles using accelerometry. **Results:** Participants in both groups were well matched for all variables at baseline. Following the intervention period, functional ability was significantly improved in the WBV group (1.22(0.19) to 0.92(0.19), p=0.02). Hip BMD was significantly reduced in the CON group (0.97(0.05) to 0.84(0.05) $g.cm^{-2}$, p=0.01), while no significant loss was seen in the WBV group (1.01(0.05) to 0.94(0.05) $g.cm^{-2}$, p=0.50). Furthermore fatigue levels were improved in the WBV group after three months (4.4(0.63) to 1.1(0.65), yet remained unchanged in the CON group at both follow ups (p=0.01). RA disease activity did not change in either group at either follow up. Ten minute bouts of light to moderate physical activity were significantly reduced in the CON group over the intervention period (2.8(0.61) to 1.8(0.64) bouts per day, p=0.01), and were preserved in the WBV group (3.1(0.59) to 3.0(0.61) bouts per day, p=0.70). **Conclusion:** Intermittent WBV shows promise for sustained improvements in functional ability, for attenuating loss of bone mass at the hip, as well as for improving fatigue levels in patients with established RA.

Introduction:

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune condition resulting in severe pain, joint erosion, and decreased functional ability. RA also predisposes patients to developing osteoporosis. This may be as a result of the presence of circulating inflammatory cytokines inherent to the disease, the decreased mobility of RA patients, resulting in a sedentary lifestyle, or due to certain medications taken to treat the disease. Levels of mobility and functional ability have been shown to be related to BMD; as have age, stature, and sex, independently of RA disease (48-49).

The health assessment questionnaire (HAQ), which is a disease specific measure of functional ability for patients with RA, is an increasingly widely used outcome measure for RA (33). A large qualitative study conducted in female patients with RA found that patients report pain and decreased functional ability as having the most widespread effect on their daily lives (154). Inability to perform normal daily activities not only decreases quality of life, but also further perpetuates a sedentary lifestyle. Moderate and vigorous habitual physical activities have known osteogenic effects (155). Conversely, increased time spent in sedentary behaviours has been independently associated with poor bone mass in healthy populations (156). Functional ability as assessed by the HAQ, has been shown to be improved following certain exercise interventions conducted on patients with RA (90), yet there is still no consensus on the most feasible type of exercise intervention for patients with chronic pain and , often, severe disability.

Whole body vibration (WBV) comprises of a mechanical vibration platform that produces energy via forced oscillation. The vibratory waves are then transferred to an individual via propagation through the feet, legs, trunk and the head (93). WBV has been shown to increase

strength, balance, and to improve pain in various chronic conditions (97). Furthermore, studies conducted in postmenopausal women (99), as well as in younger healthy populations (96), and athletes with low BMD (100), have shown WBV to improve BMD, particularly at the hip and spine (101-102). Although the exact mechanisms whereby WBV increases BMD are unclear, it is likely that there are multiple mechanisms at play. Whole body vibration has been shown to activate fluid flow in the caniliculi and lacunae of bone matrix in rats (103), in a manner proportional to loading frequency. This fluid flow creates shear stress on the plasma membrane of osteocytes, bone lining cells, and osteoblasts, which therefore respond accordingly (56). WBV thus activates mechanostransduction in bone and stimulates osteogenesis (103). Furthermore, muscle forces have been shown to exert the greatest osteogenic stimulus on bone, and the generation of these forces through vibration stimulus is likely a contributor to the skeletal adaptations that occur (94).

Exercise interventions in RA are not always feasible, specifically bone loading exercises which need to be dynamic in order to increase bone mass (56). Whole body vibration is safe, requires minimal effort and movement, has positive effects on muscle strength, and stimulates bone loading. Further, WBV has been shown to decrease fatigue levels in patients with fibromyalgia (157), and to decrease pain levels in patients with knee osteoarthritis (158). WBV has not, to the best of our knowledge, been used as a form of exercise in patients with RA. Furthermore, of the studies which have used WBV in other populations, none have examined whether WBV induced effects are sustained following an intervention. The aims of our study were therefore to determine the effects of a WBV programme on functional ability in participants with established RA, as well as to determine any effects WBV may have on BMD, RA disease activity, health related quality of life (HRQoL) as assessed by fatigue and pain levels, physical activity profiles, and body composition.

Methods:

Study Design:

Thirty nine Black, female participants with stable and established RA were initially enrolled in this study, and were assigned (using an alternating method) into either a WBV group who underwent the WBV intervention, or a control (CON) group who continued with their normal daily activities. The study was conducted at one site (Chris Hani Baragwanath Academic hospital). All eligible participants were initially assessed at enrollment (baseline assessment). Participants then underwent the relevant intervention for a three month period, following which all participants returned for a follow up assessment (three month assessment) in order to determine the effects of the WBV intervention in comparison to the CON group. Thereafter, all participants continued with their normal activities for another three months, following which a three month post intervention assessment was conducted (six month assessment) in order to determine whether any WBV effects were sustained.

Participants:

Participants were recruited from the Rheumatology Clinic at the Chris Hani Baragwanath Academic Hospital in Soweto, South Africa. Consenting participants were included if they were older than 18 years, had been diagnosed with RA (according to the 1987 ACR criteria (123)) at least three years previously, were on stable drug therapy (prednisone <10mg/day), and had been for at least three months previously. Participants were excluded if they were HIV+, were using bisphosphonates or corticosteroid injections, had any co-morbidities that could potentially impact on physical activity levels, were using assistive walking devices, had previously had hip or knee joint replacement surgery, and if they were pregnant. Ethical

approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (M130113)

Outcome Assessments:

Functional Ability assessment

Participants were assessed for functional ability using the modified Health Assessment Questionnaire (mHAQ). The mHAQ is a well validated, self-administered, RA specific questionnaire that assesses functional ability in eight domains of daily activities where scores range from 0 (no disability) to 3 (severe disability) (29).

BMD assessment

Participants underwent a Dual X-Ray Absorptiometry (DXA) scan to assess Bone Mineral Density (BMD) and body composition. All participants were assessed for site specific areal BMD at the left hip, lumbar spine (L1-L4), and whole body. All scans were performed by the same qualified technician on the same machine (Hologic QDR 4500A, Hologic, Boston, USA). The DXA operator was not aware of the assignment of the participants to the WBV or CON group. The machine was routinely calibrated throughout the study, and a phantom spine was scanned daily to determine coefficients of variation of the machine. Coefficients of variation during the course of the study for spine BMD was 0.31%. Z scores were calculated based on the total hip BMD, and according to the reference values in the NHANES database (145).

Disease Activity and HRQoL measurements

All participants were assessed for disease activity using the Clinical Disease Activity Index (CDAI) by the same physician (MAM, who was blinded to the assignment of participants to

either the WBV group or CON group). Participants were also asked to assess their fatigue levels using a Lickert scale anchored at 0 (not tired at all) and 5 (the most tired I have ever felt), as well as their pain anchored at 0 (no pain) and 5 (unbearable pain).

Physical Activity

Participants were fitted with an Actical (Respironics Inc., Murrysville, PA, USA) accelerometer (for the assessment of habitual physical activity) worn on a Velcro belt on the right hip for a one week period at baseline (assessment 1), at the end of the intervention (assessment 2) and three months after that (assessment 3). Participants then returned the accelerometer to the clinic one week later. Participants were instructed to wear the accelerometer all day, and to remove the device only while sleeping, bathing or showering. Actical data were recorded in one minute epochs and data were reduced by removing only full days of non-wear time as observed by a full day of zero activity counts. Sleep time was removed by direct observation of the data (159), and only the remaining data were considered as wear time. Three days of wear time with a minimum of 10 hours of wear time per day was required for inclusion in the analysis (25).

Activity Data

The Actical accelerometer records activity counts, which (based on the number of counts per epoch), are then classified by the inbuilt Actical software into thresholds of intensity; namely sedentary (0-100 counts), light activity (100-1485 counts), moderate activity (1486-5557 counts), and vigorous activity (≥5558 counts). Data were thus considered "active" data if a minute epoch had an activity count that was greater than 100 (i.e.: light to moderate/vigorous activity). Activity bouts were then calculated as the number of times per day that at least 10 consecutive minutes of "active data" were recorded (160). The number of times that

sedentary activity was "broken up" was calculated as the number of times per day that a sedentary minute epoch (<100 counts) was followed by at least one active minute epoch (>100 counts); and these data were thus considered as a break in sedentary time (144). Data were reported as average activity counts per day; percentage of time spent in sedentary, light, moderate and vigorous activity thresholds; average number of activity bouts per day, as well as average number of sedentary breaks per day. Participants wore the same Actical at both visits in order to minimise inter-device variability.

Body Composition

Height (measured to the nearest mm using a stadiometer (Holtaine, UK)), and body mass (measured to the nearest 100g using a standard digital scale (Dismed, USA) were measured. From these measurements Body Mass Index (BMI) was calculated. Total lean and fat mass measurements were obtained from the body composition component of the whole body DXA scan. Skeletal muscle index (SMI) was calculated by adding appendicular lean mass (left and right- arm and leg- lean masses), and dividing by height squared (147).

Intervention:

The WBV group performed two 15 minute session per week of supervised WBV, which consisted of ten repetitions standing on the vibration plate for 60 seconds, followed by a 30 second rest period. This intermittent protocol was designed to increase osteogenic effects (53) and has previously been used successfully (Prioreschi et al, 2012). All WBV training was performed on the same vertical synchronous vibration plate (DKN XG 5.0, DKN Technology, California, USA), and vibration was set at 3mm amplitude and a frequency of 30Hz in all instances. Participants were taught the correct posture while on the vibration plate in order to maximise the vibration effect and standardise procedure; and all sessions were

monitored by the primary investigator for compliance and accuracy. All participants in the WBV group completed the required 24 sessions of WBV training. The CON group was instructed to continue with their normal daily activities for the three month period, and compliance was assessed using accelerometry before and after the intervention period to ensure that activity levels did not change.

Statistical Analysis:

All analyses were conducted using Stata 12/IC 12.0 for Mac (StataCorp LP, College Station TX, USA). Student's unpaired t-tests were used to compare HAQ, BMD, physical activity, patient characteristics, and RA disease activity data between the WBV group and CON group at baseline. Thereafter, to assess the effect of the intervention on the primary and secondary outcomes, individual linear mixed models were used for each dependent variable. Random intercepts were used to account for within person correlation of repeated measures. To test a priori hypothesis, the estimated mean scores at each time point (three- and six months post baseline) were contrasted with baseline values. Model fit was assessed using residual plots and diagnostics. The WBV was then divided into responders and non-responders using percentage change from baseline in whole body BMD and mHAQ. Various outcome variables were then compared in these two groups using student's unpaired t-tests. All values are mean (SD) or mean (SEM), and a p value ≤ 0.05 was considered significant. A sample size calculation (ß=0.10) showed that at a 5% level (using an SD of 0.19) we would require a sample of 8 participants in each group in order to detect a minimum clinically important difference of 0.22 in HAQ score (161) with a power of 90%.

Results:

Patient Characteristics:

Following enrollment, there were eight dropouts due to participants not being able to attend the required assessments. These participants were not different from completers in terms of age, disease duration, or functional ability ($p>0.05$). Therefore, 31 participants allocated to the WBV group (n=16) or the CON group (n=15) completed the study. There were no participants lost to follow up after the three month intervention period, however at the six month assessment (3 month post intervention period), one patient in the WBV group and three participants in the CON group were lost to follow up due to no longer being interested in participating, or not being able to attend the required assessments (Figure 2.8).

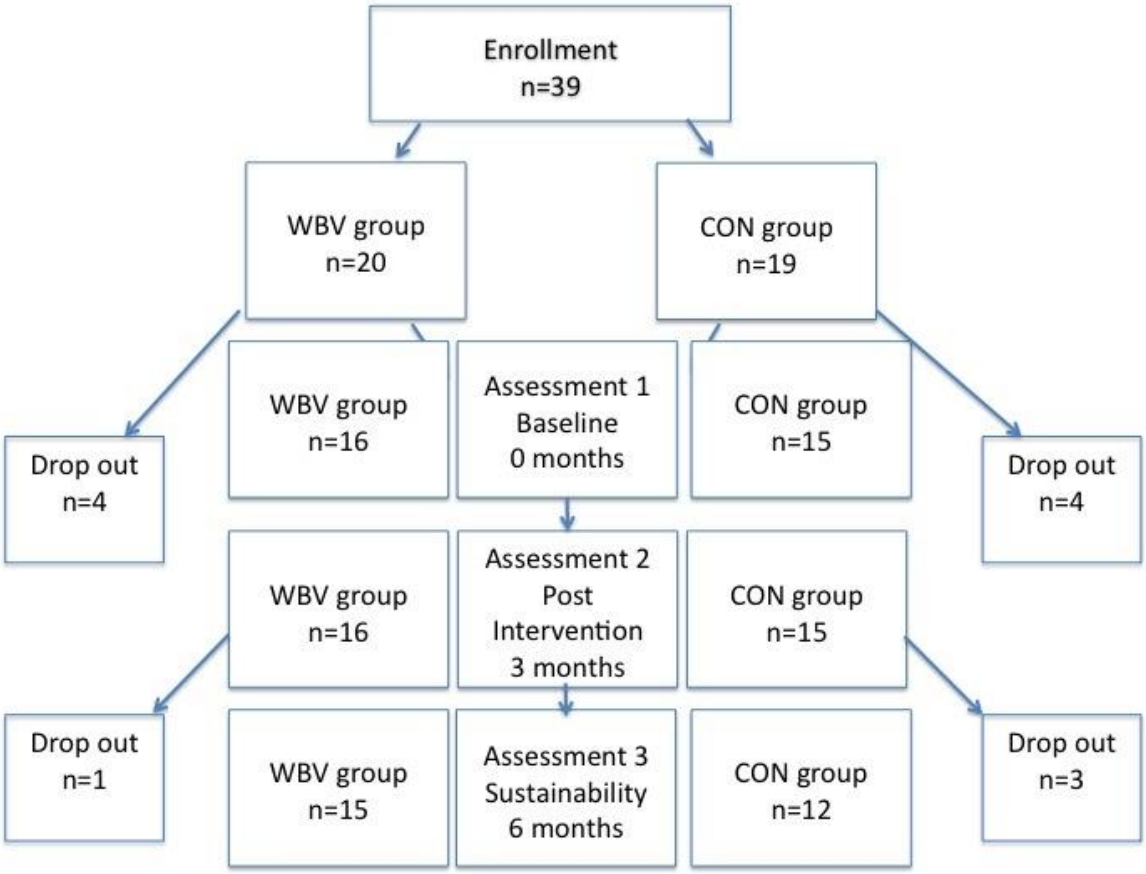


Figure 2.8. Number of study participants initially enrolled and followed up at each assessment time point.

Upon entry into the study, there were no differences between the WBV group and the CON group for any of the variables measured as shown in Table 2.9. There were no significant differences between the WBV and CON groups for BMD at any of the sites measured at baseline, specifically at the total hip (1.01(0.16)g.cm^2 vs. 0.97(0.20)g.cm^2 , p=0.50), lumbar spine (0.92(0.16)g.cm^2 vs. 0.91(0.15)g.cm^2, p=0.84), and whole body sites (1.09(0.12)g.cm^2 vs. 1.07(0.14)g.cm^2, p=0.70). Furthermore, there were no significant differences between average physical activity levels (p=0.63, data shown in Table 2.10).

Table 2.9. Patient characteristics at baseline in the WBV group and CON group. Data are mean(SD).

	WBV (n=16)	CON (n=15)	p value
Age (years)	51(10)	52(12)	0.81
Disease duration (years)	10(11)	12(8)	0.54
Height (m)	1.59(0.07)	1.55(0.08)	0.16
Body mass (kg)	85.24(21.96)	80.76(23.63)	0.59
Lean body mass (kg)	45.65(8.48)	42.11(7.96)	0.25
% body fat	42(7)	41(6)	0.55
CDAI	11(9)	8(6)	0.33
mHAQ (max. of 5)	1.22(0.67)	1.13(0.86)	0.74
Pain (max. of 3)	4(3)	4(3)	0.92
Fatigue (max. of 5)	4(3)	3(3)	0.35

* p<0.05

Functional Ability

Baseline, post intervention (three month)-, and six month follow up data for mHAQ, BMD, RA and physical activity variables are presented in Table 2.10. In the WBV group, mHAQ was significantly decreased (p=0.02) at the six month follow up as compared to baseline, while no changes were observed in the CON group at either the three or six month assessments (Figure 2.9).

Table 2.10. Mixed model analysis between the WBV and CON groups at baseline, three- and six month assessments. Data are mean(SEM)

		WBV Mean (SEM)			CON Mean(SEM)			Mixed models analysis (p value)		
Outcomes	Variables	Baseline	3 month	6 month	Baseline	3 month	6 month	group	Time	Group*time
Functional Ability	mHAQ (max. of 3)	1.22(0.19)	1.02(0.19)	0.92(0.19)*	1.13(0.20)	1.06(0.20)	1.17(0.20)	0.79	0.25	0.18
Bone	Whole Body BMD ($g.cm^2$)	1.09(0.03)	1.10(0.03)^	1.10(0.03)*	1.07(0.03)	1.07(0.03)	1.05(0.03)*	0.47	0.15	<0.01
	Hip BMD ($g.cm^2$)	1.01(0.05)	0.96(0.05)	0.94(0.05)	0.97(0.05)	0.94(0.05)	0.84(0.05)*	0.37	0.01	0.50
	Spine BMD ($g.cm^2$)	0.92(0.04)	0.92(0.04)	0.92(0.04)	0.91(0.04)	0.91(0.04)	0.91(0.04)	0.87	0.84	0.74
	Z score	0.32(0.32)	-0.14(0.32)	-0.15(0.33)	0.10(0.34)	-0.11(0.34)	-0.82(0.38)*	0.38	0.02	0.50
HRQoL and Disease activity	Fatigue (/5)	4.4(0.63)	1.1(0.65)*	3.7(0.67)	3.4(0.67)	3.7(0.75)	3.7(0.72)	0.40	0.04	0.01
	Pain (/5)	3.90(0.69)	3.07(0.71)	4.75(0.71)	4.00(0.71)	4.83(0.71)	4.75(0.78)	0.40	0.34	0.26
	CDAI	11.10(1.88)	9.59(1.88)	9.64(1.94)	8.20(1.94)	10.33(1.94)	8.80(1.94)	0.59	0.91	0.56

Physical activity	Average AC (/day)	7296(828)	7424(864)	7194(884)	6984(855)	6613(855)	6385(971)	0.53	0.85	0.88
	Sedentary (%/day)	68(2.6)	68(2.8)	70(2.8)	69(2.7)	70(2.8)	71(3.2)	0.67	0.57	0.96
	Light (%/day)	21(1.70)	21(1.80)	19(1.85)	20(1.75)	20(1.75)	20(2.08)	0.80	0.65	0.92
	Moderate (%/day)	11(1.27)	11(1.32)	10(1.35)	11(1.31)	10(1.31)	9(1.47)	0.59	0.50	0.91
	Vigorous (%/day)	0.02(0.01)	0.02(0.01)	0.01(0.01)	0.01(0.01)	0.01(0.01)	0.00(0.01)	0.31	0.75	0.91
	Breaks sedentary time (#/day)	61(3.3)	63(3.5)	63(3.6)	67(3.4)	60(3.4)*	61(4.0)	0.90	0.59	0.14
	Activity bouts (#/day)	3.1(0.59)	3.4(0.60)	3.0(0.61)	2.8(0.61)	2.1(0.61)*	1.8(0.64)*	0.26	0.14	0.16
Body Composition	BMI (kg/m^2)	34(2.1)	34(2.1)	33(2.1)*	34(2.2)	34(2.2)	34(2.2)	0.84	0.58	0.05
	Fat mass (kg)	37(3)	36(3)	35(3)*	31(3)	32(3)	35(3)*	0.43	0.44	<0.01
	Lean mass (kg)	46(2)	46(2)	45(2)	42(2)	42(2)	40(2)*	0.13	<0.01	<0.01
	SMI	7.8(0.39)	8.0(0.39)^	8.0(0.39)^	7.7(0.40)	7.9(0.40)	7.4(0.41)*	0.64	0.02	<0.01

Breaks in sedentary time are adjusted for % total sedentary time at each time point.
mHAQ – modified health assessment questionnaire, BMD – bone mineral density, HRQoL – health related quality of life, CDAI – clinical disease activity score, AC – activity counts, BMI - body mass index, SMI – skeletal mass index.

* Significantly different from baseline ($p<0.05$)
^ Trend towards significant difference from baseline ($p<0.07$)
Shading refers to reference cell

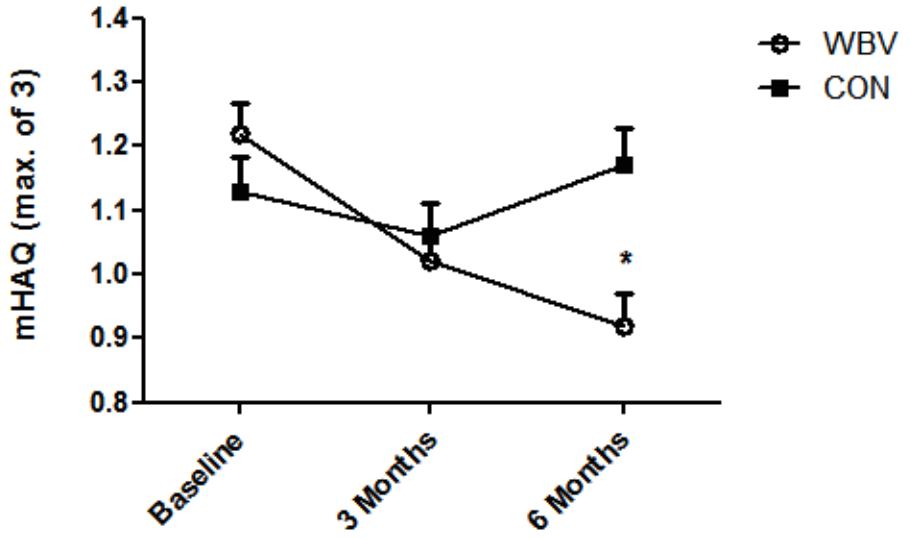


Figure 2.9. Changes in functional ability as assessed by the modified Health Assessment Questionnaire (mHAQ) for the whole body vibration group (WBV) and the control group (CON) at baseline, post intervention (3 months as well as at the 6 month follow up. Data are mean(SEM).
* Significantly different from baseline ($p<0.05$)

Bone mineral density

A significant interaction for time and group was evident for whole body BMD ($p<0.01$), whereby there was a trend towards a significant ($p=0.06$) increase in whole body BMD for the WBV group after the intervention, and BMD was significantly increased at the six month follow up compared to baseline ($p=0.05$) (Table 2.10). In the CON group, whole body BMD was significantly decreased ($p<0.01$) at the six month follow up compared to baseline (Figure 2.10). Hip BMD was significantly lower ($p=0.01$) in the CON group at the six month follow up compared to baseline. No changes were observed for the WBV group. There were no significant changes in spine BMD over the study period for either of the groups. There was a significant time effect ($p=0.02$) for Z scores (calculated at the hip site), in the CON group at the six month follow up from baseline ($p=0.02$). No significant changes were observed in the WBV group.

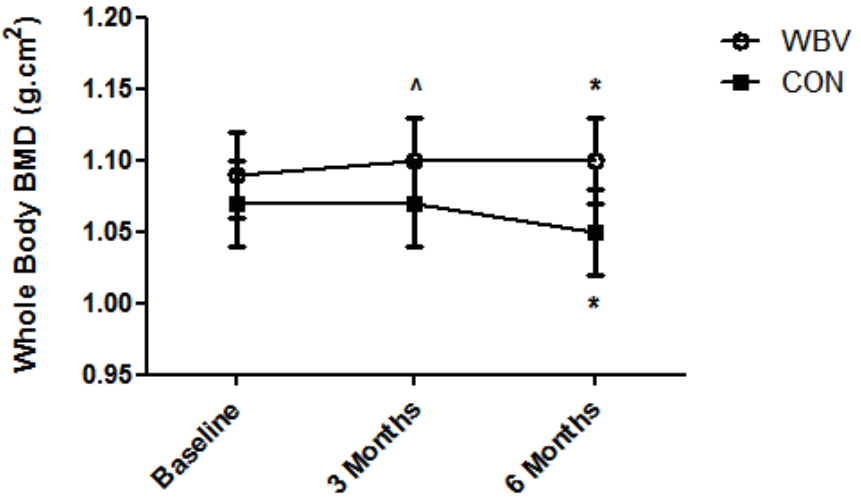


Figure 2.10. Changes in whole body bone mineral density (BMD) from baseline, post intervention (3 month assessment) as well as at the 6 month follow up in the whole body vibration group (WBV) and control group (CON). Data are mean(SEM).
* Significantly different from baseline ($p<0.05$)
^ Trend towards significant difference from baseline ($p<0.07$)

HRQoL and Disease Activity

Table 2.10 shows the significant time effect ($p=0.04$), as well as a significant group by time interaction ($p=0.01$) for fatigue levels, where fatigue was significantly decreased ($p<0.01$) in the WBV group at the three month follow up as compared to baseline, however this effect was not sustained at the six month follow up. No changes were observed in the CON group for fatigue levels over the study period. There were no significant changes in CDAI scores over the intervention period for either of the groups. There were no significant changes in pain levels over the study period for either of the groups.

Physical activity

No significant main effects, or group by time interactions were observed for physical activity levels (Table 2.10). No significant changes were evident in either group for average activity counts per day, or percentage of time spent in sedentary, light, moderate or vigorous activity

over the study period. However, in the CON group, the number of breaks in sedentary time (after adjusting for percentage of time in sedentary activity at each time point) were significantly decreased ($p=0.05$) at the three month follow up as compared to baseline. In the CON group, there was also a significant decrease ($p=0.05$) in number of activity bouts per day at the three month follow up as compared to baseline; and this effect was sustained at the six month follow up compared to baseline assessment ($p=0.01$). No changes were observed in the WBV group for number of breaks in sedentary time, or number of active bouts.

Body composition

Table 2.10 shows the significant group by time interaction effects for BMI ($p=0.05$) and fat mass ($p<0.01$), both were significantly decreased in the WBV group at the 6 month follow up as compared to baseline ($p=0.02$, $p=0.01$ respectively). In the CON group, fat mass was significantly increased ($p<0.01$) at the six month follow up from baseline. Lean mass and SMI showed significant time effects ($p<0.01$, and $p=0.02$ respectively), as well as significant (both $p<0.01$) group by time interactions. Lean mass was significantly ($p<0.01$) decreased in the CON group at the six month follow up as compared to baseline. SMI showed a trend towards significant increase ($p=0.06$) in the WBV group at the three month follow up from baseline, which was sustained at the 6 month follow up from baseline ($p=0.08$), while in the CON group SMI was significantly decreased ($p<0.01$) at the three month follow up from baseline, and the six month follow up from baseline ($p=0.02$).

Effects of intervention on individual responses:

Figure 2.11 shows the percentage change from baseline in whole body BMD for each participant. The WBV group showed significant increases in BMD (0.90(0.53)%) compared to the CON group who showed decreases in BMD (-0.66(0.52)%) over the intervention

period (p=0.04). In a sub-analysis, the WBV group was divided into responders (≥0% change from baseline) and non-responders (<0% change from baseline) according to percentage change in whole body BMD. Eleven out of the 16 participants were found to be responders (67%) within the WBV group. mHAQ improved significantly more in the responders (43(41)%) than in the non-responders, who experienced decreases in mHAQ over the three month intervention (-38(9.2)%), p=0.02. Furthermore, responders showed significantly greater increases in number of activity bouts per day (27(77)%) than the non-responders, who experienced decreases in activity bouts (-40(36)%), (p=0.08). No other significant differences were found between these two sub-groups for any of the other variables measured. The WBV group was then divided into responders and non-responders in a similar manner, but now according to change in mHAQ (Figure 2.12). Ten out of the 16 participants were found to be responders (63%). Here, responders showed significantly greater improvements in lean mass (1.4(1.7)%) then the non-responders who showed decreases in lean mass (-2.2(2.3)%), p<0.01. No other differerences were seen between responders and non-responders for mHAQ.

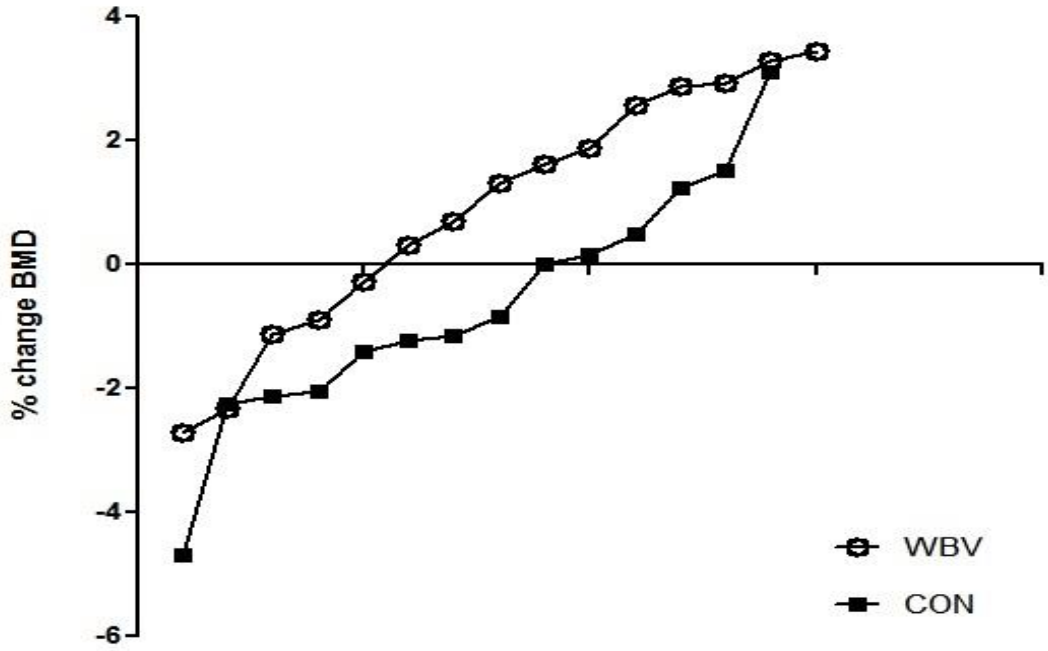


Figure 2.11. Percentage change in whole body bone mineral density (BMD) from baseline to post intervention (three month assessment) for each participant in the whole body vibration group (WBV) and the control group (CON).

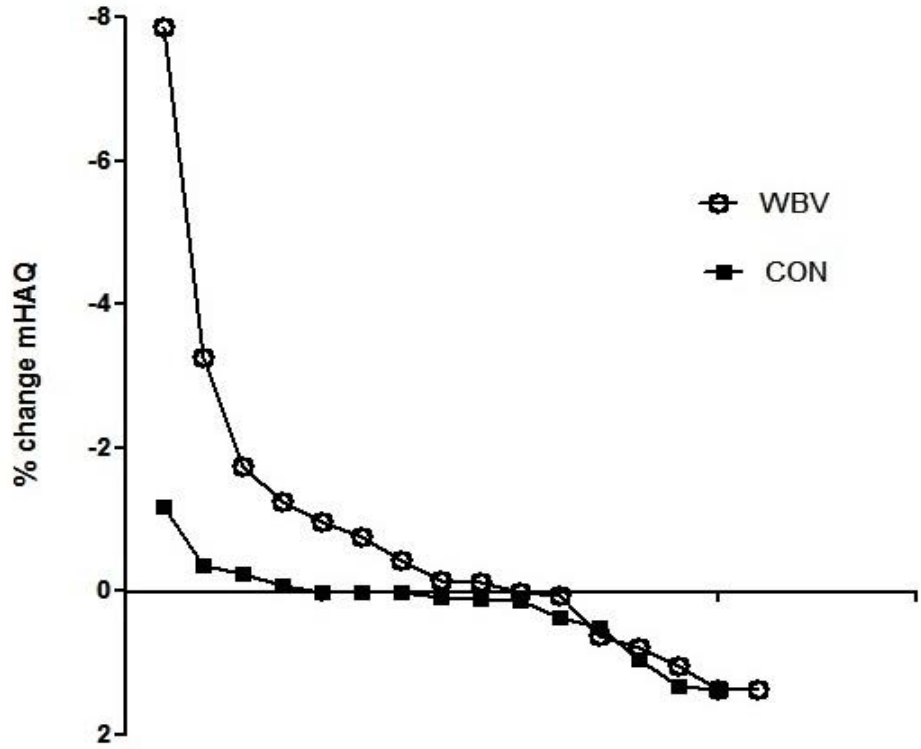


Figure 2.12. Percentage change in functional ability as assessed by the modified Health Assessment Questionnaire (mHAQ) from baseline to post intervention (three month assessment) for each participant in the whole body vibration group (WBV) and the control group (CON).

Discussion:

Our 12 week WBV intervention in participants with established, stable RA had positive effects on functional ability, BMD, HRQoL, physical activity profiles, and body composition in comparison to participants in the control group. Importantly, mHAQ scores started to decrease in these patients with established RA who underwent WBV, and were significantly improved at the six month follow up. Also of importance is the maintenance of increased whole body BMD observed in the WBV group after cessation of WBV, as well as the attenuation of loss of hip BMD in the WBV group in comparison to the losses of hip BMD observed in the control group. Our findings lend support to the possibility that WBV may be useful for improving certain HRQoL outcomes such as fatigue, which may in turn have contributed to the increase in functional ability observed; therefore having a protective effect on bone health in patients with RA.

Participants in the WBV group became more likely to have normal daily function following the intervention, which is an important target for RA treatment (8). Improvements in HAQ have been shown in previous exercise interventions performed in groups of people with RA, which utilised either strength training (162-163), or aerobic exercise programmes (91). In the present study, changes in mHAQ were significantly higher for those who exhibited an osteogenic response to the WBV intervention than for those whose bone mass did not respond; implying that improvements in mHAQ may be related to improvements in BMD in this cohort.

Various WBV interventions have produced promising results with regards to improving BMD. Versheuren et al in 2004 (102) and Rubin et al in 2004 (101) showed that WBV training for a six months and one year period respectively, was able to significantly increase hip BMD in a group of postmenopausal women. Rubin and colleagues further showed improvements in spine BMD in their cohort. Prioreschi et al in 2012 were also able to show increases in hip BMD and attenuated losses of spine BMD in a group of road cyclists who participated in 10 weeks of intermittent WBV (100).

In an RA population, where bone health is severely compromised and continuously deteriorating, maintenance of BMD is often the goal of treatment. The present study showed that participants who participated in a WBV exercise intervention experienced sustained improvements in whole body BMD, as well as preserved hip BMD levels, while the CON group experienced losses in BMD at both these sites. Hip BMD has been shown to be the best predictor of fracture risk at any site (132), and maintenance of these levels could therefore contribute to a decreased fracture risk. WBV was well tolerated by the present cohort, and could potentially be a feasible intervention for BMD in patients with RA that does not require the vigorous, high-impact movements that are usually required to increase BMD (yet are often not feasible in this population).

Notwithstanding the stable disease activity that was maintained by the patients, fatigue levels were significantly improved following the WBV intervention (although these effects were not maintained at the six month follow up). Fatigue and 'feeling well' are important outcomes in RA, and two of the most relevant improvements to note following treatment interventions in RA (8, 164). The constant presence of fatigue greatly alters the ability to lead a functional life. The present effects on fatigue are similar to the effects observed in cohorts of patients with fibromyalgia and osteoarthritis following WBV – who experienced decreases in fatigue levels and pain levels respectively (157), (158). It is difficult to separate the true effects of WBV from the presence of a group intervention, however it is clear that our WBV intervention was able to modify patients' sense of well-being, and their HRQoL even though disease activity was not significantly altered. WBV in the present study has shown similar effects on well being as have been shown following aerobic and resistance exercise interventions in patients with RA (89-91).

Previous research has shown that higher levels of habitual physical activity in patients with RA are correlated with improved fatigue levels, as well as functional ability (143). Recent literature has focused on the beneficial effects of breaking up sedentary time (regardless of overall activity levels) on health (165), as well as the beneficial effects of being more active (often requiring activity to be

performed in 10 minute bouts) (4). Although overall physical activity remained unchanged before and after the intervention for both groups, there were important changes observed in the patterns of physical activity that should be considered. The CON group decreased the number of times they broke up their sedentary time and also had fewer bouts of activity following the intervention, yet these activity profiles were maintained in the WBV group. Furthermore, those who exhibited an osteogenic response to the WBV intervention had significantly greater increases in activity bouts after the intervention compared to non-responders. Limiting sedentary time has been shown to have beneficial effects on bone health (156). It is possible that the WBV intervention, by means of decreasing fatigue levels, allowed patients to modify their habitual physical activity profiles and to start engaging in less sedentary behaviors, thereby becoming more functional.

Participants who underwent WBV also lost a significant amount of body mass (specifically body fat) during the intervention period, and experienced a significant increase in lean mass. This is likely due to the ability of WBV to increase oxygen consumption, energy expenditure, and neuromuscular performance (166) through continuously effecting eccentric and concentric muscular contractions (167). Sarcopenia, in combination with osteoporosis, greatly increases the risk of obtaining a fracture (168). Participants in the WBV group maintained their lean muscle mass, and showed a trend towards improving SMI (an indicator of sarcopenia), while both SMI and lean mass were decreased in the CON group. Participants who showed an improvement in functional ability after undergoing WBV intervention also had significantly greater increases in lean mass than non-responders. This is likely also related to improved physical activity profiles. Whole body vibration has previously been shown to decrease BMI, as well as body fat (as measured by DXA) in obese women (167), and has been shown to slow fat acquisition in rodent models (169). In both of these studies a decrease in fat mass following WBV was accompanied by an increase in BMD or bone mineral content, which was not observed in the relevant control group. Although lower body mass is a known risk factor for low bone mass (48), and it is therefore assumed that higher body mass is protective of BMD, recent studies have suggested that obesity may have an inverse relationship

with BMD (170), and that fractures that occur in obese populations should be considered 'fragility fractures' (171). Potentially, obesity is distinct from 'high body mass' in terms of the effect it has on bone health; and should still be avoided in patients with RA, as is recommended in the general population. Our results suggest that WBV therapy may be useful in decreasing body mass, as well as increasing lean muscle mass in patients with RA.

Our study has strengths and limitations. The intervention was implemented by a multidisciplinary team of community practitioners and has potential to be disseminated for a wider reach. Additionally, all assessments were repeated after the completion of the intervention, and we have thus demonstrated that some of the benefits of WBV in participants with RA can be sustained for at least three months. Furthermore, our attrition rates were very low and the program was well tolerated within this population. Unfortunately we did not make qualitative assessments of the intervention and thus cannot negate the possibility that group participation had an effect on various outcomes, as opposed to the WBV itself. Furthermore, the short duration of the intervention, as well as the limited sample size (although significantly powered) limits the conclusions that can be drawn. Lastly, since the intervention ran over a year period with staggered recruitment, the effects of the colder temperatures in winter may have altered various pain and well-being outcomes; however participants were recruited in an alternating manner, which would limit the potential differences between groups.

In conclusion, participants with stable and established RA, who underwent a WBV intervention showed improvements in functional ability, and preservation of bone mass at the hip and whole body, and preservation of lean muscle mass. Participants who participated in the WBV intervention also had improved fatigue levels, yet no changes in RA disease activity were observed. Furthermore, participants in the WBV group maintained their habitual physical activity profiles throughout the assessment period. WBV offers a useful and affordable adjunct therapy with

sustained effects in patients with established RA for the improvement of functional ability and attenuation of bone loss, as well as improvement of fatigue.

Competing Interests:

The authors declare that they have no competing interests.

Author Contributions:

AP conceived the study, collected all data, drafted the manuscript and analysed the data. MAM was the primary physician involved in assessing all patients. MT was involved in conceptualisation of the study design. JAM was involved in conceptualisation of the study as well as analysis of the data. All authors read and approved the final manuscript.

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Chapter 3. Discussion and Conclusions

The most exciting phrase to hear in science, the one that heralds new discoveries, is not Eureka (I found it!) but rather, "hmmm… that's funny…"

-Isaac Asimov

3.1 Introduction

This thesis aimed to examine three main objectives. Firstly, to determine whether accelerometry can be used as an objective measurement of habitual physical activity levels in patients with RA, secondly to determine the associations between habitual physical activity levels and RA disease, and the factors contributing to this relationship, and thirdly, to determine whether WBV therapy can be used as an effective intervention for increasing functional ability and BMD, as well as for improving other disease outcomes in patients with RA. These objectives were addressed in more detail in Chapter 1, where after the results of the studies that were conducted in order to assess these objectives were presented in Chapter 2. Each study was also individually discussed with reference to the current literature in Chapter 2. This chapter will briefly discuss and summarise the results of this thesis as a whole, and will conclude with the main findings, as well as the contribution that the thesis hopes to make to the current literature.

3.2 Objectives and Results Summary

Table 3.1. Summary of objectives and corresponding results of the thesis

Objective	**Location**	**Findings**
1 To objectively quantify habitual physical activity levels in patients with RA in comparison to a healthy population	Study 1	Accelerometry was identified as a feasible means to objectively measure habitual physical activity levels in a group of female patients with RA and was used in all subsequent studies. Patients with RA were found to be significantly more sedentary and to undertake significantly less light activity than their healthy counterparts. Diurnal differences in daily activity were also found, most likely due to late afternoon fatigue and early morning joint stiffness.
2 To ascertain any associations between habitual physical activity levels and disease activity in patients with RA	Study 1	Habitual physical activity levels were found to be positively associated with functional ability as assessed by HAQ. Furthermore, patients who were more physically active had better HRQoL, (specifically fatigue levels), than the less physically active patients. Associations were evident between habitual physical activity levels and disease activity in these patients i.e.: increased physical activity was associated with better RA disease outcomes
3 To determine changes in habitual physical activity levels in patients newly diagnosed with RA in response to commencement of DMARD therapy	Study 2	Habitual physical activity levels were significantly improved following DMARD therapy. Diurnal differences in daily activity were no longer evident between the RA patients and healthy counterparts following DMARD therapy
4 To determine predictive factors causing the changes seem in disease activity in response to commencement of DMARD therapy in patients with RA	Study 2	Changes in CRP and joint stiffness were predictive of changes in habitual physical activity levels in patients with RA

5 To determine the associations between habitual physical activity levels and bone health in patients with RA	Study 3	Higher levels of habitual physical activity were found in patients with normal bone mass in comparison with those with low bone mass, highlighting the relationship between increased habitual physical activity and bone mass in patients with RA
6 To determine the effects of a WBV therapy intervention on functional ability and bone health, as well as on disease activity and habitual physical activity levels in patients with RA	Study 3	Patients who participated in a WBV therapy intervention experienced increased functional ability, as well as increased whole body BMD; maintained their hip BMD, and reported having a improved fatigue levels following the intervention in comparison to a control group of RA patients who continued with their normal activities for three months

3.3 Summary of contributions to the field:

The literature review presented in Chapter 1 identified several gaps in the literature, broadly: The lack of a clear outcome measure for physical activity in RA, the lack of understanding of the associations between physical activity and disease activity in RA, the lack of data regarding habitual activity levels in RA, as well as the inconclusive evidence and prescriptions for exercise interventions in RA. The results of the studies conducted in this thesis have given novel insights into the habitual activity levels of patients with RA, as well as the benefits of being more physically active for this population; using accelerometry as an effective outcome measure for physical activity in RA. Increased levels of physical activity have repeatedly shown beneficial effects on fatigue, functional ability and well being. This is important for physicians and patients alike, as these results indicate that a vigorous exercise intervention is not necessarily needed to experience improvements in HRQoL. Patients should be encouraged to be more habitually active i.e.: breaking up their sedentary time more frequently by standing up more often and incorporating light walking into their daily routines. Patients should spend less time sitting and should aim to move around as much as possible. While enforced exercise is also important, most patients are not able, or unwilling to participate in exercise programmes. Increasing habitual activity levels may be a means to counteract this problem, while still conferring beneficial effects on well being. The beneficial effects of increased habitual activity levels were also evident on bone health in patients with RA. However, increased habitual activity is most likely not enough to increase BMD, or attenuate BMD loss to any large degree in patients with RA, who progressively lose BMD throughout the course of their disease. A bone loading intervention is required, and WBV proved to be effective in attenuating loss of BMD at the hip (as well as improving HRQoL and functional ability). WBV therapy does not require conventional 'exercising', and is therefore a very feasible option for these patients. These data provide a therapeutic option for these patients, that is effective and provided sustained improvements in BMD. These findings will be discussed in more detail in the next section.

3.4 Discussion:

The results presented in this thesis contribute to the current understanding of the effects of physical activity in RA. Overall this thesis has provided evidence as to the beneficial effects of greater levels of physical activity on RA disease activity, as well as on other important RA outcomes such as HRQoL, functional ability, and bone health. These findings are in agreement with numerous other studies that have found physical activity to have beneficial effects for patients with RA. The work presented in this thesis provides novel objective assessments of physical activity, which allowed for in depth analyses of activity patterns in these patients, as well as in the first evidence of WBV therapy as an intervention for patients with RA.

3.4.1 Methodological themes emanating from this thesis:

The main methodological theme emanating from this thesis was objective measurement of physical activity in RA. It is well known that patients with RA are forced into a sedentary lifestyle due to the pain and deformities that are common characteristics of their disease. Previous studies assessing physical activity levels in RA have generally made use of subjective physical activity questionnaires, which have downfalls with regards to their accuracy, as well as language barriers that my exist. In the first study presented in this thesis, accelerometry was used as an objective measure of physical activity, and whether or not these measurements could be translated into clinical practice was investigated. A better understanding of patterns and detailed information about patterns of physical activity may be valuable information for consideration in the design of successful interventions that target certain physical activity behaviours or times of day (172-173). The use of accelerometry allowed for the extent of the sedentary lifestyles of patients with RA to be objectively characterised for the first time in comparison to a healthy control group. Furthermore, this study established the use of accelerometry as a feasible, well tolerated measure of habitual physical activity levels in this group of patients, and was thus used throughout the subsequent studies that emanated from this thesis.

Additionally, accelerometry was able to identify distinct periods of lower physical activity levels during the day (in the early morning, as well as the late afternoon) in patients with RA that were not evident in control participants. These were attributed to two common symptoms of RA: early morning joint stiffness and late afternoon fatigue, which have long been described by clinicians, but had not until this point been empirically shown as periods of lower physical activity. Previously, people with osteoarthritis have been shown to have a stronger association between fatigue and objectively measured physical activity (using the Actical) than with pain and physical activity (174), yet these associations had not, until this research, been shown in populations with RA. This further highlights the ability of accelerometry to capture activity patterns and provide a thorough understanding of daily habitual activities in this cohort.

In Study three, we were also able to use accelerometry to assess patterns of physical activity in patients with RA, by monitoring the number of times that patients were breaking up their sedentary time, as well as the number of ten minute bouts of light to moderate activity that were being undertaken per day. These assessments are extremely novel in RA, and allow for an in depth understanding of how physical activity levels are affected by the disease, as well as how they can be modified. With the growing interest into understanding sedentary behaviour as an independent contributor to negative health outcomes, these novel assessments are now proving to be crucial in the understanding of physical activity and inactivity in healthy, as well as diseased populations. Increased time spent being sedentary is associated with many health problems, such as metabolic and cardiovascular disorders, and this risk may be greater than the risk of not meeting the required guidelines of physical activity (117, 165). Patients with RA are already at greater risk of cardiovascular morbidity (75, 79), emphasising the importance of breaking up time spent in sedentary activity with light and moderate activities such as walking at various intensities. Prolonged periods of sedentary behaviour means unbroken periods of muscular unloading and therefore loss of contractile stimulation (117), which is compounded by the decreased strength and

muscular atrophy that occurs in patients with RA. This research provides novel insights in to the benefits of using accelerometry as an objective measure of physical activity in RA, as well as the techniques that can be employed to determine detailed patterns of physical activity in these patients. This work has clinical, as well as practical applications for physicians, researchers, and patients alike.

3.4.2 Empirical themes emanating from this thesis:

The first empirical theme emanating from this research was the beneficial effects of higher levels of habitual physical activity for patients with RA. The first study of this thesis showed that patients with RA are very sedentary, spending almost three quarters of their awake day being sedentary. Once able to objectively measure the sedentary lifestyles of these patients to such an extent, it became interesting to try and identify associations between physical activity levels and other routinely measured disease activity outcomes. All three studies make inroads towards showing that patients who were more habitually active fare better on other RA outcomes, specifically their functional ability, and their fatigue levels. Increased physical activity has been shown to reduce pain and improve function (84, 122), decrease swollen and tender joint counts (71), decrease morning stiffness and fatigue using a graded aerobic exercise programme (72), as well as to improve self impression (175). Similarly to previously conducted studies (however now making use of an objective measurement of physical activity), we were able to show that improved functional ability is positively correlated with increased physical activity levels, as is an improved sense of well being.

In Study 2, the relationship between improved disease activity and improved habitual physical activity levels, with no actual exercise intervention or verbal promotion of physical activity taking place could mean that in addition to the improvements seen in disease activity measures after commencing drug therapy, patients spontaneously alter their habitual physical activity. Increasing habitual physical activity levels, which is potentially more sustainable than an exercise intervention

in an arthritic population, could lead to improved functional ability, allowing for a more vigorous exercise intervention to be implemented at a later stage.

Furthermore, although the associations between physical activity and bone health have been shown in multiple previous studies (138, 149), Study 3 was able to objectively monitor these physical activity levels, and thus to objectively explore the relationships between different intensities of physical activity on bone health for the first time. Furthermore, we were able for the first time to determine the effects of not meeting recommended physical activity guidelines on bone health, and showed that patients who were classified as meeting the required physical activity guidelines also had significantly better Z scores than those who did not, implying less bone loss due to the disease process rather than normal aging. Once again, the link between being habitually active and having better disease outcomes was clear in this population. These findings are important for patients with RA who have been shown to be more sedentary than their healthy counterparts (143).

These three studies contributed to the understanding of the beneficial effects of physical activity for patients with RA, and make it clear that higher levels of habitual physical activity need to be prescribed for patients with RA. From these studies, better recommendations can start being made regarding the intensity and duration of physical activity that is required for beneficial effects to be seen. Specifically and most importantly, patients should aim to be less sedentary. Further evidence examining the effects of enforcing such prescriptions in more varied cohorts of patients still needs to be obtained.

The next empirical theme emanating from this thesis was the use of WBV therapy as an exercise intervention for patients with RA. Upon reading the multiple studies that have been conducted examining the effects of various exercise interventions in RA (summarised in Chapter 1, Section 1.10), a clear gap in the literature was discovered. Very few studies have designed exercise interventions aimed specifically at increasing, or attenuating the loss of BMD; even though

osteoporosis is a major problem for patients with RA. Furthermore, many of the exercise interventions that have been conducted in this population are not necessarily feasible in a South African context, nor for patients who are disabled and have chronic pain.

Since WBV therapy is easy to use, does not require much movement or impact, and is feasible in a South African context, it could possibly be a means to allow patients with RA to exercise safely and regularly. Whole body vibration had not previously been used as an intervention for RA, yet previous studies have shown the beneficial effects of WBV on HRQoL in diseases such as fibromyalgia and osteoarthritis (157-158). Furthermore various WBV interventions have produced promising results with regards to improving BMD (100-102).

Patients who participated in WBV therapy experienced significant decreases in fatigue levels and improvements in the functional ability. They also had increases in their muscle mass, and decreases in their fat mass, which were not evident in the control group. Patients in control group also had decreases in their habitual physical activity levels, which were preserved in the group who participated in WBV therapy. Whole body vibration therapy was able to elicit similar benefits to previous exercise intervention studies, without requiring strenuous exercising. This study also showed that WBV was able to maintain physical activity patterns, while they decreased in the participants who did not partake in WBV. The beneficial effects of higher levels of physical activity and lower levels of sedentary activity have been shown in the previous studies in this thesis, as well as in the current literature, and the importance of maintaining these levels in patients with RA is thus clear.

Furthermore, patients who had participated in the WBV intervention experienced improvements, or attenuations in the loss of their bone health. These findings are similar to what has been shown in healthy, as well as postmenopausal populations. Versheuren et al in 2004 (102) and Rubin et al in 2004 (101) showed that WBV training for a six month and one year period respectively, was able to

significantly increase hip BMD in a group of postmenopausal women. Rubin and colleagues further showed improvements in spine BMD in their cohort. Prioreschi et al in 2012 were also able to show increases in hip BMD and attenuated losses of spine BMD in a group of road cyclists who participated in 10 weeks of intermittent WBV (100). These findings have not previously been shown in populations with RA. We were further able to show for the first time that there were associations between improved bone health and improved functional ability in this population, likely alluding to the mechanisms behind the increases seen in bone mass. Whole body vibration was well tolerated and safe, and could therefore be implement in routine care for these patients.

This research makes inroads towards understanding the potential uses of WBV in RA, yet more research is required to fully understand the mechanisms, effects, and optimal duration and frequency of this kind of intervention. However, the potential implications of such a simple, feasible intervention are great, for South Africa, as well as for other low to middle or high income countries. These needs to be further explored so that better exercise recommendations can be made.

The results of the studies conducted in this thesis provide novel insights into the relationship between physical activity and health in RA. We have assessed novel techniques for objectively measuring physical activity in RA, and through this have contributed to the understanding of how physical activity levels affect various outcomes in RA. We have also provided evidence for a novel form of exercise therapy that could be used in RA, which is affordable, sustainable, effective, and feasible in this population. Sedentary behavior is a global problem, but more so in a population where the effects of a sedentary lifestyle are amplified by the disease process. This thesis helps in the understanding of these associations, as well as in providing solutions to improve the problems that exist in the treatment of RA.

3.5 Limitations:

There were various limitations to this research, the details of which were discussed in relation to each specific study (Chapter 2). This research was focused only on females, and therefore the results presented cannot necessarily be extrapolated to males. However the incidence of RA is known to be much higher in females than in males (26), thus this research maintains far reaching implications for the population. The lack of data with regards to occupation or employment status could be considered a limitation of the first two studies. Furthermore, throughout these studies we excluded patients who were severely disabled or using assistive walking devices, which limits the extrapolations we can make to RA patients needing to make use of such devices. However these patients would most likely not be able to make use of WBV therapy, nor partake in standard physical activity, and further research would need to be done into feasible interventions for such patients.

The placement of the Actical on the hip could be considered a limitation of our studies. The hip placement meant that only lower limb movement could be measured, however the manufacturer recommends hip placement for accuracy of detection of movements in multiple planes. Our studies were particularly focused on habitual, ambulatory physical activity, and thus hip placement was the most sensible option.

Another limitation is the potential confounding effect of menopausal status on bone health, which was not assessed in this study. The short duration of the WBV intervention may have had an impact on the size of the effect seen, and future studies should examine the effects of a long term WBV intervention. Lastly, the limited sample sizes within the various studies could be considered a limitation, however each study was significantly powered for the primary outcome of that study. Study 3 could have benefitted from a larger sample size that would have ensured more participants in each bone mass group, yet a power analysis conducted retrospectively showed that the study was, in fact, significantly powered. The WBV intervention could have benefitted from a larger sample

size in order to ensure significant power of the mixed model analysis, yet was significantly powered in order to detect univariate changes from baseline.

Upon retrospective evaluation of the intervention process, it became evident that it was unfortunate that I had not made any qualitative assessments of the WBV intervention, which limited the conclusions that can be made with regards to the possibility of group participation having an effect on various outcomes, as opposed to the WBV itself. This should be considered in future research.

3.6 Future Research and Direction:

The results presented in this study open up new questions that remain to be considered as well as new ideas as to the direction that should be taken in dealing with physical activity behaviours and interventions for patients with RA. Firstly, the interactions that have been made evident between habitual physical activity levels and HRQoL (including fatigue and pain), as well as disease activity, functional ability, and even bone health; allude to the importance of incorporating an objective measure of physical activity, such as accelerometry, into the routinely measured clinical outcomes assessments of RA. In doing so, clinicians would be better equipped to understand the extent to which patients are limited by their disease, as well as to monitor improvements more robustly. Since the ability to be functional has such weighting in the lifestyle of the patient, being able to objectively assess this would add hugely to understanding of individualised responses to the disease. Furthermore, the ability of accelerometry to detect periods of fatigue and early morning joint stiffness provides an even more comprehensive assessment of the patients' well being.

Secondly, this research points to the importance of promoting physical activity as a means to improve various symptoms of RA, as discussed throughout this thesis. It is evident that, although exercise interventions have been shown to have great benefits on disease activity in RA; simply increasing habitual physical activity levels can lead to significant improvements. This means that patients should, before even considering enforced exercise programmes, be encouraged to start

being more active. This includes breaking up sedentary time more frequently by standing up from sitting or lying down as often as possible, as well as light walking, and finally incorporating small bouts of moderate activity such as a walk around the block every day (although this does not seem to impart as much benefit as simply being less sedentary). These guidelines are simple, easy to explain, and most importantly, easy to incorporate into daily life even when faced with a chronic pain condition. Importantly, although simplistic, the effects of such changes seem to be great. Thereafter, targeted interventions can be included, such as a WBV intervention. These interventions need to be designed for people who cannot properly exercise, and as such, WBV seems to be ideal.

Future research should also aim to better understand the effects of different intensities of exercise on RA. It is clear that breaking up sedentary time is important for health, and that bouts of activity seem to have greater effects than sporadic activity. Furthermore it seems that decreased sedentary activity and increased light activity have greater effects on certain outcomes than increased moderate activity in patients with RA. This needs to be further explored in the context of RA so that better exercise prescriptions can be made.

Lastly, the importance of a qualitative assessment on the effects of an exercise intervention should not be overlooked. It is possible that some of the effects on well being that were achieved can be attributed to participating in a monitored programme, being 'looked after' twice weekly, and having a 'support group' of sorts to talk to and befriend. Furthermore, having a reason to get up and leave the house twice a week surely has an impact on feelings of well being, as well as habitual activity levels (many patients reported that, when not at their sessions with me or at their doctors appointments, they would stay in bed or at home all day- having no reason or motivation to do otherwise). Patients self reported during informal discussions with myself that they appreciated having me care for them and being aware of the pain they felt on a daily basis. Certain patients would come to sessions that were not their own, simply to visit and chat to their friends who were exercising, and most patients stayed long after their session was finished just to socialise. These

effects and lifestyle modifications cannot be ignored. These ideas should be explored in a well designed, qualitative analysis, and should be included in the designs of future interventions in order to allow for cumulative effects.

Given all of these findings and the limitations of the studies that have already been conducted, there are two main branches of research I would like to examine in more detail in future studies. Firstly, I would like to design a more long term, targeted WBV intervention designed at improving bone mass, and to examine the effects of such an intervention on sub groups of patients with varying levels of bone health in comparison to the standard drug therapy for bone health within each sub group. Secondly, I would like to design a habitual physical activity intervention, aimed at educating patients about the benefit of being more physically active, and specifically designed to break up sedentary time. Both of these studies would require quantitative analysis in order to determine the impact of the group participation and individualised care, over and above the intervention itself.

3.7 Conclusion:

The results of these studies have given novel insights into the habitual activity levels of patients with RA, as well as evidence as to the benefits of being more physically active for this population. In conclusion, this thesis provides results that should encourage patients with RA to become more habitually active, and should encourage physicians to incorporate these ideas, as well as objective measurement of these outcomes, into standard treatment of RA. If patients cannot, or will not exercise; WBV therapy should be offered as a therapeutic tool. Ultimately, awareness of these associations, and the benefits that can be achieved through simple means, could vastly improve the quality of life for patients afflicted with a painful, chronic condition where any small improvement to their symptoms could greatly change their lifestyles.

Chapter 4: References

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Chapter 5: Appendices

Appendix 1 – Study 1 Subject Information Sheet and Informed Consent

Previously diagnosed patients

INFORMATION SHEET

Objective measures of physical activity in patients with rheumatoid arthritis

Hello. My colleagues (Dr Joanne McVeigh, Dr Ingrid Avidon) and I, Alessandra Prioreschi, are doing research on physical activity in patients with rheumatoid arthritis (RA). In this study we want to learn whether we can monitor physical activity levels in patients with RA and whether these physical activity levels change in response to rheumatoid medication. This study involves research only and does not provide routine care or treatment for your disease. The study is being conducted to learn more about the effects of rheumatoid arthritis on physical activity and quality of life in patients on RA medication, which could help with future treatment of RA patients.

If you are already enrolled in either the GREAT or CHERISH study at the Rheumatology clinic (Chris Hani Baragwanath Hospital) we would like to invite you to participate in our research study. If you agree to participate in our study, you will be asked to do the following as described below:

1. When you visit the clinic for your routine GREAT or CHERISH study visit, you will once again complete the routine set of questionnaires for the GREAT or CHERISH study as you have done on a previous visit. This set of questionnaires will take approximately 40 minutes to complete. An investigator or a nurse will be available to help you complete the questionnaire if you require assistance. At this visit, you will be given an activity data logger (a small, match-box size device) that you will be asked to wear on a belt on your hip during the day and on your wrist at night. The logger is small and light and will not cause any discomfort. The logger will measure your physical activity (how much you are moving) during the day and during the night. You will be asked to begin wearing the logger the next day and will wear the logger for two weeks (during the day on your hip and at night on your wrist). The logger cannot be worn when you swim, shower or bath and should be removed at these times. After the two week period you will be asked to return the logger to the clinic.

2. In addition, for the full two weeks, you will be asked to complete a simple pain questionnaire at night before going to bed which will ask about your pain during the day and will take one minute to complete. In the morning when you wake up you will be asked to complete a questionnaire about your sleep and pain during the night (how well you slept and whether your sleep was disturbed by pain). This questionnaire will take two minutes to complete.

3. After the two weeks, when you return the activity data logger as well as the pain and sleep questionnaire to the clinic, you will be asked to complete a physical activity questionnaire. The questionnaire asks questions about your physical activity over the previous two weeks

and will take approximately 15 minutes to complete. As before, an investigator or a nurse will be available to help you complete the questionnaire if you require assistance.

The details of your involvement are given below:

Visit 1 to clinic

- Complete the routine GREAT or CHERISH questionnaires
- Receive the activity data logger

During the two weeks

- Wear the data logger on your waist during the day and on your wrist at night.
- Remove the logger when you bath or shower or swim.
- Complete the pain questionnaire at night and sleep and pain questionnaire in the morning.

Visit 2 to clinic (after two weeks)

- Return data logger to the clinic.
- Return pain and sleep questionnaires
- Complete physical activity questionnaire

Please note that all participation is voluntary and you will be free to leave the trial at any time. You participation in this study, as well as any personal information is strictly confidential. You will receive a code and all your records and information will be filed under this code. If you wish, your individual results will be made available to you. We have obtained approval for this study from the Committee for Research on Human Subjects of the University of the Witwatersrand. If, after reading this information, you decide against participating in the study please be assured that this will not impact on you negatively in any way. If you have any further questions please ask me (Alessandra, 0741887545) or one of my colleagues at the clinic.

You will not be paid to participate in this study, but your transport and, where necessary, refreshment costs will be reimbursed adequately according to the Medicines Control Council of South Africa. We would like to invite you to participate in this study and to confirm your willingness to do so by signing the consent form overleaf. If you agree to participate, you are allowing us to use any information obtained from the questionnaires filled out in the GREAT or CHERISH studies, as well as allowing us access to your medical records as needed.

Sincerely,

Alessandra Prioreschi, Ingrid Avidon, Joanne McVeigh

If you require any information regarding your **rights as a research participant** you may contact Prof. Cleaton-Jones, Chairperson of the University of the Witwatersrand, Human Research ethics Committee (HREC), which is an independent committee established to protect the rights of research participants at (011) 7172301

Contact details of researcher: Alessandra Prioreschi (011) 7172115

If you have **questions about this trial you should** first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the Medicines Control Council (MCC) South Africa at:

The Registrar
Medicines Control Council SA
Department of Health
Private Bag X828

PRETORIA, 0001

INFORMED CONSENT:

- I hereby confirm that I, _____, have been informed by the study co-ordinator about the nature, conduct, benefits and risks of the study: "Objective measures of physical activity in patients with rheumatoid arthritis".
- I have also received, read and understood the above written information sheet regarding the study.
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study, as well as data from the ORBIT/GREAT/CHERISH studies can be processed in a computerised system by the University of the Witwatersrand, School of Physiology, or on their behalf.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.

PARTICIPANT:

Printed Name Signature Date and Time

I, _____, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

STUDY CO-ORDINATOR:

Printed Name Signature Date

TRANSLATOR

Printed Name Signature Date

Appendix 2 – Study 2 Subject Information Sheet and Informed Consent

Newly diagnosed patients

INFORMATION SHEET

Objective measures of physical activity in patients with rheumatoid arthritis

Hello. My colleagues (Dr Joanne McVeigh, Dr Ingrid Avidon) and I, Alessandra Prioreschi, are doing research on physical activity in patients with rheumatoid arthritis (RA). In this study we want to learn whether we can monitor physical activity levels in patients with RA and whether these physical activity levels change in response to rheumatoid medication. This study involves research only and does not provide routine care or treatment for your disease. The study is being conducted to learn more about the effects of rheumatoid arthritis on physical activity and quality of life in patients on RA medication, which could help with future treatment of RA patients.

If you are already enrolled in the ORBIT study at the Rheumatology clinic (Chris Hani Baragwanath Hospital) we would like to invite you to participate in our research study. If you agree to participate in our study, you will be asked to do the following as described below:

4. When you visit the clinic for your routine ORBIT study visit, you will be asked to complete the routine set of questionnaires for the ORBIT study. This set of questionnaires will take approximately 40 minutes to complete and asks questions about your health, use of medication, pain, functional ability and mood. An investigator or a nurse will be available to help you complete the questionnaire if you require assistance. At this visit, you will be given an activity data logger (a small, match-box size device) that you will be asked to wear on a belt on your hip during the day and on your wrist at night. The logger is small and light and will not cause any discomfort. The logger will measure your physical activity (how much you are moving) during the day and during the night. You will be asked to begin wearing the logger the next day and will be asked to wear the logger **until** you receive your prescribed medication which should be one-to-two weeks later. When you do start to take your medication please do not wear the logger and return it to the clinic. The logger cannot be worn when you swim, shower or bath and should be removed at these times.

5. In addition, for the full one-or-two weeks when you wear the logger, you will be asked to complete a simple pain questionnaire at night before going to bed which will ask about your pain during the day and will take one minute to complete. In the morning when you wake up you will be asked to complete a questionnaire about your sleep and pain during the night (how well you slept and whether your sleep was disturbed by pain). This questionnaire will take two minutes to complete.

6. After the one-to-two weeks, when you return the activity data logger as well as the pain and sleep questionnaire to the clinic, you will be asked to complete a physical activity

questionnaire. The questionnaire asks questions about your physical activity over the previous one-to-two weeks and will take approximately 15 minutes to complete. As before, an investigator or a nurse will be available to help you complete the questionnaire if you require assistance.

7. Three months later, when you return to the clinic for your routine visit as part of the ORBIT study, we will ask that you to once again complete the set of questionnaires for the ORBIT study, wear the activity data logger for a full two weeks, complete the pain and sleep questionnaires during the two weeks and complete the physical activity questionnaire when you return the data logger after the two weeks.

The details of your involvement are given below:

Visit 1 to clinic

- Complete the routine ORBIT questionnaires
- Receive the activity data logger

During the one-t0-two weeks

- Wear the data logger on your waist during the day and on your wrist at night.
- Remove the logger when you bath or shower or swim.
- Complete the pain questionnaire at night and sleep and pain questionnaire in the morning.

Visit 2 to clinic (after one-to-two weeks)

- Return data logger to the clinic.
- Return pain and sleep questionnaires
- Complete physical activity questionnaire

Visit 3 to clinic (three months later)

- Complete the routine ORBIT questionnaires
- Receive the activity data logger

During the two weeks

- Wear the data logger on your waist during the day and on your wrist at night.
- Remove the logger when you bath or shower or swim.
- Complete the pain questionnaire at night and sleep and pain questionnaire in the morning.

Visit 4 to clinic (after the two weeks)

- Return data logger to the clinic.
- Return pain and sleep questionnaires
- Complete physical activity questionnaire

Please note that all participation is voluntary and you will be free to leave the trial at any time. You participation in this study, as well as any personal information is strictly confidential. You will receive a code and all your records and information will be filed under this code. If you wish, your individual results will be made available to you. We have obtained approval for this study from the Committee for Research on Human Subjects of the University of the Witwatersrand. If, after reading this information, you decide against participating in the study please be assured that this will not impact on you negatively in any way. If you have any further questions please ask me (Alessandra, 0741887545) or one of my colleagues at the clinic.

You will not be paid to participate in this study, but your transport and, where necessary, refreshment costs will be reimbursed adequately according to the Medicines Control Council of South Africa.

We would like to invite you to participate in this study and to confirm your willingness to do so by signing the consent form overleaf. If you agree to participate, you are allowing us to use any information obtained from the questionnaires filled out in the ORBIT study, as well as allowing us access to your medical records as needed.

Sincerely,

Alessandra Prioreschi, Ingrid Avidon, Joanne McVeigh

If you require any information regarding your **rights as a research participant** you may contact Prof. Cleaton-Jones, Chairperson of the University of the Witwatersrand, Human Research ethics Committee (HREC), which is an independent committee established to protect the rights of research participants at (011) 7172301

Contact details of researcher: Alessandra Prioreschi (011) 7172115

If you have **questions about this trial you should** first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the Medicines Control Council (MCC) South Africa at:

The Registrar
Medicines Control Council SA
Department of Health
Private Bag X828
PRETORIA, 0001

INFORMED CONSENT:





- I hereby confirm that I, _____, have been informed by the study co-ordinator about the nature, conduct, benefits and risks of the study: "Objective measures of physical activity in patients with rheumatoid arthritis".
- I have also received, read and understood the above written information sheet regarding the study.
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study, as well as data from the ORBIT/GREAT/CHERISH studies can be processed in a computerised system by the University of the Witwatersrand, School of Physiology, or on their behalf.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.

PARTICIPANT:

Printed Name Signature Date and Time

I, _____, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

STUDY CO-ORDINATOR:

Printed Name Signature Date

TRANSLATOR

Printed Name Signature Date

Appendix 3 – Study 3 Information Sheet and Informed Consent

INFORMATION SHEET

Whole Body Vibration therapy in patients with Rheumatoid Arthritis

Hello, my name is Alessandra Prioreschi. My colleagues (Dr Joanne McVeigh and Dr Mohammed Tikly) and I are doing research on whole body vibration therapy and resistance training in patients with rheumatoid arthritis (RA). This research will form part of my PhD degree at the University of the Witwatersrand. In this study we want to learn whether we can use whole body vibration therapy to help improve your bone and muscle strength, and to maybe help your pain as well. This study involves research only and does not provide routine care or treatment for your disease. The study is being conducted to learn more about the effects of whole body vibration on rheumatoid arthritis disease, osteoporosis and physical activity in patients on RA medication, which could help with future treatment of RA patients.

We would like to invite you to participate in our research study. If you agree to participate in our study, you will be assigned into one of two groups: a Whole Body Vibration group, or a Control group. The details of your involvement are described below depending on the group you are in:

8. You will first be asked to visit the clinic for an assessment. You will be asked to complete a set of questionnaires used routinely in RA diagnosis and therapy. This set of questionnaires will take approximately 20 minutes to complete and asks questions about your health, use of medication, pain, functional ability and mood. An investigator or a nurse will be available to help you complete the questionnaire if you require assistance. You will also have some measurements taken including height and weight, flexibility and balance, strength measurements and cardiovascular health. We will also measure your bone mineral density using the same DXA scan that was used to diagnose your osteoporosis. In this scan you need to lie still for approximately 15 minutes while a qualified technician operates the machine. The measurements will not hurt or be uncomfortable. A DXA scan exposes you to very small amounts of radiation (less than a normal X-Ray), and is considered safe for adults. Lastly, you will be given an activity data logger (a small, match-box size device) that you will be asked to wear on a belt on your hip during the day. The logger is small and light and will not cause any discomfort. The logger will measure your physical activity (how much you are moving) during the day. You will be asked to begin wearing the logger the same day and will be asked to wear the logger for one full week until you return to the clinic for your next visit. The logger cannot be worn when you swim, shower or bath and should be removed at these times. The first assessment will last approximately 2 hours.

9. **If you are in the Whole Body Vibration group**:
   One week after your first assessment, you will start with your whole body vibration sessions at the clinic. Whole body vibration is a type of therapy that is used to increase your bone density, and improve your osteoporosis. Whole body vibration therapy may also improve your pain and tiredness. All you need to do in these sessions is stand on the vibration plate

for 10 sets of one minute sessions. The total session will last 15 minutes. I will be with you for each session to show you how to use the plate and in case you need help. The vibration therapy does not cause any pain, and if you feel uncomfortable at any point you are free to stop and a doctor will be available if you need one. You will need to come for these sessions twice a week for 12 weeks which will total 24 sessions of vibration therapy. We will either organize transport for you, or reimburse you per kilometer for your travel expenses on each day of travel.



This image shows you how you will be asked to stand on the vibration plate

If you are in the Control group:

One week after your first assessment, you will return the data logger to the clinic. For the following 12 weeks you will not be required to do anything except to carry on with your normal daily routine. You should continue to take your medication as usual and you should not change your normal daily activities (including exercising) for the 12 weeks period.

Following the 12 weeks of whole body vibration, or your normal routine (depending on which group you are assigned to), you will be asked to come to the clinic to repeat all the measurements that were done at the first assessment, including completing the questionnaires, and the DXA scan. You will also be asked to wear the data logger on your hip for another one week. Therefater you will continue with your normal activities for another 12 week period, no matter which group you are in. We will then call you in for a final assessment were all the same measurements that were done at the first assessment will be repeated, including completing the questionnaires, and the DXA scan. You will also be asked to wear the data logger on your hip for another one week

Once you return the data logger after the one week period of wearing it, your involvement in this study will be complete. The results of your measurements and scans will be available to you at your request.

The details of your involvement are given below:

Visit 1 to clinic

- Complete the routine questionnaires
- Receive the activity data logger
- Undergo measurements
- DXA scan

During the first week

- Wear the data logger on your waist during the day for one week.
- Remove the logger when you bath or shower or swim.

During the six weeks (**Whole Body Vibration group**)

- Come to the clinic two to three times a week for whole body vibration therapy

During the six weeks (**Control group**)

- Continue with your normal daily routine
- Continue taking your medication as normal
- Do not change your daily activities during this time

Visit 2 to the clinic

- Complete the routine questionnaires
- Receive the activity data logger
- Undergo measurements
- DXA scan

During the six weeks (**Whole Body Vibration group**)

- Continue with your normal daily routine
- Continue taking your medication as normal
- Do not change your daily activities during this time

During the six weeks (**Control group**)

- Continue with your normal daily routine
- Continue taking your medication as normal
- Do not change your daily activities during this time

Final visit to the clinic

- Complete the routine questionnaires
- Receive the activity data logger
- Undergo measurements
- DXA scan

Please note that all participation is voluntary and you will be free to leave the trial at any time. You participation in this study, as well as any personal information is strictly confidential. You will receive a code and all your records and information will be filed under this code. If you wish, your individual results will be made available to you. We have obtained approval for this study from the Committee for Research on Human Subjects of the University of the Witwatersrand. If, after reading this information, you decide against participating in the study please be assured that this will not impact on you negatively in any way. If you have any further questions please ask me (Alessandra, 0741887545) or one of my colleagues at the clinic.

You will not be paid to participate in this study, but your transport and, where necessary, refreshment costs will be reimbursed adequately according to the Medicines Control Council of South Africa.

We would like to invite you to participate in this study and to confirm your willingness to do so by signing the consent form overleaf. If you agree to participate, you are allowing us to use any information obtained from the questionnaires filled out in the ORBIT study, as well as allowing us access to your medical records as needed.

Sincerely,

Alessandra Prioreschi, Mohammed Tikly, Joanne McVeigh

If you require any information regarding your **rights as a research participant** you may contact Prof. Cleaton-Jones, Chairperson of the University of the Witwatersrand, Human Research ethics Committee (HREC), which is an independent committee established to protect the rights of research participants at (011) 7172301

Contact details of researcher: Alessandra Prioreschi (011) 7172140

If you have **questions about this trial you should** first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the Medicines Control Council (MCC) South Africa at:

The Registrar
Medicines Control Council SA
Department of Health
Private Bag X828
PRETORIA, 0001

INFORMED CONSENT:

- I hereby confirm that I, _____, have been informed by the study co-ordinator about the nature, conduct, benefits and risks of the study: "Whole body vibration therapy in patients with rheumatoid arthritis".
- I have also received, read and understood the above written information sheet regarding the study.
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by the University of the Witwatersrand, School of Physiology, or on their behalf.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.

PARTICIPANT:

Printed Name Signature Date and Time

I, _____, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

STUDY CO-ORDINATOR:

Printed Name **Signature** **Date**

TRANSLATOR

Printed Name **Signature** **Date**

Appendix 4 – Subject Reimbursement Letter for Study 1 and Study 2

School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, York Road Parktown, Johannesburg, South Africa, 2193
Tel: +27 11 717 2363, Fax: +27 11 643 2765

Objective Measures of Physical Activity in Patients with Rheumatoid Arthritis

This letter is to certify that _____ (volunteer) received compensation of travel expenses to the sum of R75 for travel to the Chris Hani Baragwanath Hospital for participation in the abovementioned study on the following dates _____

Volunteer sign: _____

Investigator sign: _____

Appendix 5 – Subject Reimbursement Letter for Study 3

School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, York Road Parktown, Johannesburg, South Africa, 2193
Tel: +27 11 717 2363, Fax: +27 11 643 2765

Physical Activity in Patients with Rheumatoid Arthritis

This letter is to certify that _____ (volunteer) received compensation of travel expenses to the sum of R200 for travel to the Chris Hani Baragwanath Hospital for participation in the abovementioned study (8 visits) for the month of _____

Volunteer sign: _____

Investigator sign: _____

Appendix 6 – Health Assessment Questionnaire

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)©

Name: _____ Date: _____

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
DRESSING & GROOMING				
Are you able to:				
Dress yourself, including shoelaces and buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
Stand up from a straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
Cut your own meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Devices used for Dressing (button hook, zipper pull, etc.)
☐ Built up or special utensils
☐ Crutches
☐ Cane
☐ Wheelchair
☐ Special or built up chair
☐ Walker

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and grooming ☐ Arising ☐ Eating ☐ Walking

- 1 -

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
HYGIENE				
Are you able to:				
Wash and dry your body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
Open car doors?	☐	☐	☐	☐
Open previously opened jars?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
Run errands and shop?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming or yard work?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Raised toilet seat ☐ Bathtub bar ☐ Long-handled appliances for reach

☐ Bathtub seat ☐ Long-handled appliances in bathroom ☐ Jar opener (for jars previously opened)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene ☐ Reach ☐ Gripping and opening things ☐ Errands and chores

Your ACTIVITIES: To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

COMPLETELY	MOSTLY	MODERATELY	A LITTLE	NOT AT ALL
☐	☐	☐	☐	☐

Your PAIN: How much pain have you had IN THE PAST WEEK?
On a scale of 0 to 100 (where zero represents "no pain" and 100 represents "severe pain"), please record the number below.

☐☐☐

Your HEALTH: Please rate how well you are doing on a scale of 0 to 100 (0 represents "very well" and 100 represents "very poor" health), please record the number below.

☐☐☐

Appendix 7 – Short Form-36 Questionnaire and Fatigue

INSTRUCTIONS: THIS QUESTIONNAIRE ASKS FOR YOUR VIEWS ABOUT YOUR HEALTH. THIS INFORMATION WILL HELP KEEP TRACK OF HOW YOU FEEL AND HOW WELL YOU ARE able TO DO YOUR USUAL ACTIVITIES. PLEASE BE SURE TO ANSWER EACH QUESTION BY CIRCLING ONE OF THE RESPONSES PROVIDED. IF YOU ARE UNSURE ABOUT HOW TO ANSWER A QUESTION, GIVE THE BEST ANSWER YOU CAN.

1. IN GENERAL, WOULD YOU SAY YOUR HEALTH IS:

EXCELLENT 1 VERY GOOD 2 GOOD 3 FAIR 4 POOR 5

2. COMPARED TO ONE YEAR AGO, HOW WOULD YOU RATE YOUR HEALTH IN GENERAL NOW?

MUCH BETTER NOW THAN ONE YEAR AGO 1
SOMEWHAT BETTER NOW THAN ONE YEAR AGO 2
ABOUT THE SAME AS A YEAR AGO 3
SOMEWHAT WORSE NOW THAN ONE YEAR AGO 4
MUCH WORSE NOW THAN ONE YEAR AGO 5

3. THE FOLLOWING ITEMS ARE ABOUT ACTIVITIES YOU MIGHT DO DURING A TYPICAL DAY. DOES YOUR HEALTH NOW LIMIT YOU IN THESE ACTIVITIES? IF SO, HOW MUCH?

ACTIVITIES	YES, LIMITED NO, NOT A LOT	YES, LIMITED A LITTLE
A. *VIGOROUS ACTIVITIES*, SUCH AS RUNNING, LIFTING HEAVY OBJECTS, PARTICIPATING IN STRENUOUS SPORTS	1	2
B. *MODERATE ACTIVITIES*, SUCH AS MOVING A TABLE, PUSHING A VACUUM CLEANER, BOWLING OR PLAYING GOLF	1	2
C. LIFTING OR CARRYING GROCERIES	1	2
D. CLIMBING SEVERAL FLIGHTS OF STAIRS	1	2
E. CLIMBING ONE FLIGHT OF STAIRS	1	2
F. BENDING, KNEELING OR STOOPING	1	2
G. WALKING MORE THAN A MILE	1	2
H. WALKING SEVERAL BLOCKS	1	2
I. WALKING ONE BLOCK	1	2
J. BATHING OR DRESSING YOURSELF	1	2

4. DURING THE *PAST 4 WEEKS*, HAVE YOU HAD ANY OF THE FOLLOWING PROBLEMS WITH YOUR WORK OR OTHER REGULAR DAILY ACTIVITIES AS A RESULT OF YOUR PHYSICAL HEALTH?

	YES	NO
A. CUT DOWN THE AMOUNT OF TIME YOU SPENT ON WORK OR OTHER ACTIVITIES	1	2
B. ACCOMPLISHED LESS THAN YOU WOULD LIKE	1	2
C. WERE LIMITED IN THE KIND OF WORK OR OTHER ACTIVITIES	1	2
D. HAD DIFFICULTY PERFORMING THE WORK OR OTHER ACTIVITIES (E.G., IT TOOK EXTRA EFFORT)	1	2

5. DURING THE *PAST 4 WEEKS*, HAVE YOU HAD ANY OF THE FOLLOWING PROBLEMS WITH YOUR WORK OR OTHER REGULAR DAILY ACTIVITIES *AS A RESULT OF EMOTIONAL PROBLEMS* (SUCH AS FEELING DEPRESSED OR ANXIOUS)?

	YES	NO
A. CUT DOWN THE *AMOUNT OF TIME* YOU SPENT ON WORK OR OTHER ACTIVITIES	1	2
B. *ACCOMPLISHED LESS* THAN YOU WOULD LIKE	1	2
C. DIDN'T DO WORK OR OTHER ACTIVITIES AS *CAREFULLY* AS USUAL	1	2

6. DURING THE *PAST 4 WEEKS*, TO WHAT EXTENT HAS YOUR PHYSICAL HEALTH OR EMOTIONAL PROBLEMS INTERFERED WITH YOUR NORMAL SOCIAL ACTIVITIES WITH FAMILY, FRIENDS, NEIGHBORS, OR GROUPS?

NOT AT ALL 1 SLIGHTLY 2 MODERATELY 3 QUITE A BIT 4 EXTREMELY 5

7. HOW MUCH *BODILY* PAIN HAVE YOU HAD DURING THE *PAST 4 WEEKS*?

NONE 1 VERY MILD 2 MILD 3 MODERATE 4 SEVERE 5 VERY SEVERE 6

8. DURING THE *PAST 4 WEEKS*, HOW MUCH DID *PAIN* INTERFERE WITH YOUR NORMAL WORK (INCLUDING BOTH WORK OUTSIDE THE HOME AND HOUSEWORK)?

NOT AT ALL 1 A LITTLE BIT 2 MODERATELY 3 QUITE A BIT 4 EXTREMELY 5

9. THE FOLLOWING QUESTIONS ASK HOW YOU FEEL AND HOW THINGS HAVE BEEN WITH YOU DURING THE PAST 4 WEEKS. FOR EACH QUESTION, PLEASE GIVE THE ONE ANSWER THAT COMES CLOSEST TO THE WAY YOU HAVE BEEN FEELING. HOW MUCH OF THE TIME DURING THE PAST 4 WEEKS

	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
A. DID YOU FEEL FULL OF PEP?	1	2	3	4	5	6
B. HAVE YOU BEEN A VERY NERVOUS PERSON?	1	2	3	4	5	6
C. HAVE YOU FELT SO DOWN IN THE DUMPS THAT NOTHING COULD CHEER YOU UP?	1	2	3	4	5	6
D. HAVE YOU FELT CALM AND PEACEFUL?	1	2	3	4	5	6
E. DID YOU HAVE A LOT OF ENERGY?	1	2	3	4	5	6
F. HAVE YOU FELT DOWNHEARTED AND BLUE?	1	2	3	4	5	6
G. DID YOU FEEL WORN OUT?	1	2	3	4	5	6
H. HAVE YOU BEEN A HAPPY PERSON?	1	2	3	4	5	6
I. DID YOU FEEL TIRED?	1	2	3	4	5	6

10. DURING THE *PAST 4 WEEKS*, HOW MUCH OF THE TIME HAS YOUR PHYSICAL HEALTH OR EMOTIONAL PROBLEMS INTERFERED WITH YOUR SOCIAL ACTIVITIES (LIKE VISITING WITH FRIENDS, RELATIVES, ETC.)?

ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
1	2	3	4	5

11. HOW TRUE OR FALSE IS *EACH* OF THE FOLLOWING STATEMENTS FOR YOU.

	DEFINITELY TRUE	MOSTLY TRUE	DON'T KNOW	MOSTLY FALSE	DEFINITELY FALSE
A. I SEEM TO GET SICK A LITTLE EASIER THAN OTHER PEOPLE	1	2	3	4	5
B. I AM HEALTHY AS ANYBODY I KNOW	1	2	3	4	5
C. I EXPECT MY HEALTH TO GET WORSE	1	2	3	4	5
D. MY HEALTH IS EXCELLENT	1	2	3	4	5

Fatigue Assessment

How Tired have you felt over the last week?

No at all tired	
A little tired	
Moderately tired	
Very tired	
The most tired ever felt	

Appendix 8 – SDAI and CDAI Index Form

TJC

					Shoulder					
right					Elbow		left			
					Wrist					
5	4	3	2	1	MCP	1	2	3	4	5
					PIP					
					Knee					

TOTAL TJC_____

SJC

					Shoulder					
right					Elbow		left			
					Wrist					
5	4	3	2	1	MCP	1	2	3	4	5
					PIP					
					Knee					

TOTAL SJC_____

PHYSICIAN GLOBAL ASSESSMENT

Excellent		0
Good		25
Fair		50
Poor		75
Very poor		100

EARLY MORNING STIFFNESS How long were your joints stiff this morning? (minutes) _____

PATIENT PAIN ASSESSMENT

How bad has your pain over the last week?

No pain	
Mild pain	
Moderate pain	
Severe pain	
Unbearable pain	

PATIENT GLOBAL ASSESSMENT

How has your arthritis been over last week?

Excellent		0
Good		25
Fair		50
Poor		75
Very poor		100

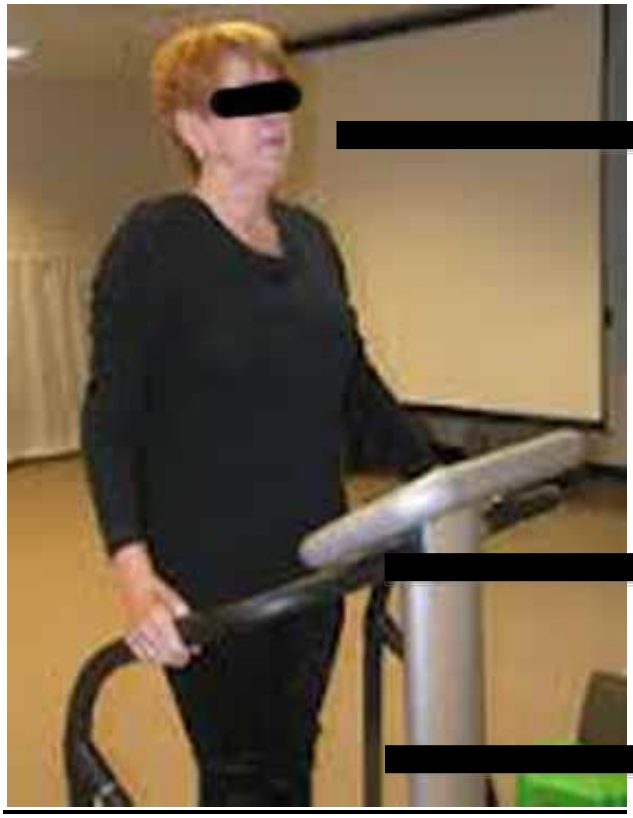
SDAI/CDAI

TJC	**SJC**	**CRP**	**patient global**	**physician global**	**SCORE**

Appendix 9 – WBV Instructions to Patients

How to use the Vibration Plate:

1. Switch on plate at the bottom
2. Stand on the plate like this:



3. Press "**Manual**"
4. Press "**Time ↓**" so that it says: 1:00 on the screen
5. Press "**Start/Stop**"
6. The plate will shake for **1 minute** then you have **30 seconds** rest on the screen
7. Before the time reaches 0:00, press "**Start/Stop**" again
8. Repeat **10** times

Appendix 10- Human Research Ethics Committee Approval Certificates

M110430

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Miss Alessandra Prioreschi

CLEARANCE CERTIFICATE	M110430
PROJECT	Objective measures of Physical Activity in Patients with Rheumatoid Arthritis
INVESTIGATORS	Miss Alessandra Prioreschi.
DEPARTMENT	School of Physiology
DATE CONSIDERED	06/05/2011
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 06/05/2011 CHAIRPERSON .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Ingrid Avidon

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

R14/49 Ms Alessandra Prioreschi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130113

NAME: (Principal Investigator) Ms Alessandra Prioreschi

DEPARTMENT: School of Physiology
Medical School

PROJECT TITLE: The Effects of a Whole Body Vibration Therapy Interventions or a Standard Resistance Training Intervention on Disease Activity and Bone Mineral Density in Patients with Rheumatoid Arthritis

DATE CONSIDERED: 25/01/2013

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr Joanne McVeigh

APPROVED BY:

Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 18/02/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Radiation and Health Physics Unit

Radiation and Health Physics Unit, Wits East Campus, Empire Road, Johannesburg Telephone: +27 (0)11 717 6931/29 Fax:+27 (0)11 717 6937
Private Bag 3, Wits 2050 South Africa: E-mail: james.larkin@wits.ac.za

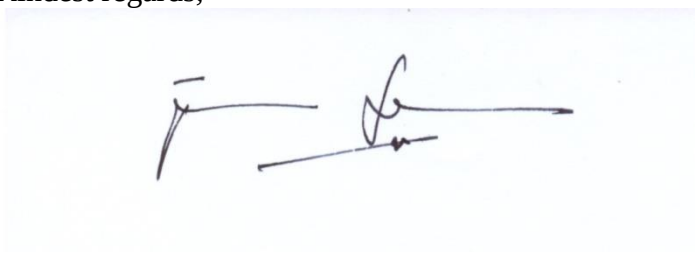
18th December 2012,

To: Prof Cleaton – Jones,
Chairman, Human Research Ethics Committee.

Re: The effect of a whole body vibration therapy intervention on disease activity and bone mineral density in patients with Rheumatoid Arthritis.
Student: Alessandra Prioreschi Student Number: 0700859D

Dear Sir,
I have reviewed the research proposal submitted by Mr. A. Prioreschi, and am satisfied that this research proposal can go forward unmodified.

Kindest regards,



James Larkin,
Director, Radiation and Health Physics Unit

Appendix 11 – Study 1

Rheumatology Advance Access published June 26, 2013

RHEUMATOLOGY 53, 300

Original article doi:10.1093/rheumatology/ket216

The clinical utility of accelerometry in patients with rheumatoid arthritis

Alessandra Prioreschi[1], Bridget Hodkinson[2], Ingrid Avidon[1], Mohammed Tikly[2] and Joanne A. McVeigh[1]

Abstract

Objectives. To assess habitual physical activity levels in patients with RA compared with healthy control participants and to compare these measures with health-related quality of life and disease activity in the RA patients.

Methods. Fifty RA patients [age 48 (13) years] and 22 BMI, sex and geographically matched control participants were recruited. Habitual physical activity was measured using an Actical accelerometer worn on the hip for 2 consecutive weeks. Patients completed the Short Form-36 (SF-36) and modified Health Assessment Questionnaires (HAQ-DI). Disease activity was assessed using the Simplified Disease Activity Index (SDAI). RA patients were further categorized as more physically active ($n = 25$) and less physically active ($n = 25$) according to their average activity counts.

Results. The RA group spent more time in sedentary activity than the control group (71% *vs* 62% of the day respectively, $P = 0.002$) and had bimodal decreases in diurnal physical activity compared with the control group in the morning ($P < 0.001$) and late afternoon ($P < 0.001$). HAQ-DI, when adjusted for age and disease duration, was negatively correlated with physical activity in the RA group ($r = -0.343$, $P = 0.026$). The more physically active patients scored better than the less physically active patients on every component of the SF-36.

Conclusion. Patients with RA lead a significantly more sedentary lifestyle than healthy controls and show diurnal differences in physical activity due to morning stiffness and fatigue. Higher levels of habitual physical activity may be protective of functional capacity and are highly associated with improved health-related quality of life in RA patients.

Key words: rheumatology, physical activity, accelerometry, functional capacity, quality of life, habitual physical activity.

Introduction

Patients with RA have been shown to have a decreased health-related quality of life (HRQoL) in comparison with the general population [1]. HRQoL (which is defined as the physical, emotional and social aspects of life that are affected by a patient's disease or their treatment) is a relevant measure of disease activity according to the WHO [2] and feeling well is an important patient outcome, along with management of pain, sleep, fatigue, emotional and physical well-being [1].

The presence of pain limits the ability of patients with RA to function normally, and as a result everyday habitual physical activity levels are reduced [3]. Exercise interventions in patients with RA have been shown to improve sense of wellbeing, decrease morning stiffness, improve sleep patterns and decrease swollen joint counts over time [4], as well as to reduce pain and improve functional ability [5]. Increasing levels of physical activity have been shown to be beneficial for patients with RA without having any adverse effects on disease activity [6]. Most studies have examined the effects of enforced exercise

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Submitted 30 July 2012; revised version accepted 2 May 2013.

Correspondence to: Alessandra Prioreschi, Department of Physiology, Faculty of Health Science, Wits Medical School, 7 York Road, Parktown 2193, Johannesburg, South Africa.
E-mail: alessandra.prioreschi@wits.ac.za

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CLINICAL SCIENCE

interventions on RA disease activity, yet surprisingly little is known about the effects of everyday, spontaneous habitual physical activity levels in patients with RA, and whether patients with increased habitual physical activity levels have better disease activity profiles or feel better. One large study by Sokka *et al.* [7] did examine self-reported physical activity levels in more than 5000 outpatients with RA in over 20 countries around the world and found that over 70% of these patients did not engage in regular physical activity at all. Furthermore, physical inactivity was more prevalent in patients with lower functionality as assessed by the HAQ. These findings remain to be elucidated using objective measures of physical activity.

Physical activity, as a functional assessment of quality of life, is difficult to assess. Questionnaires and recall diaries are commonly used but are subjective [8], and it is difficult for patients to recall their activity levels accurately, especially for light to moderate intensity activities [9]. Few studies have been performed on RA patients assessing habitual, daily physical activity levels [10]. Two studies have compared energy expenditure levels between patients with RA and controls (average energy expenditure was found to be lower in RA patients than in controls in both these studies), although both made use of subjective measures of physical activity only [11, 12].

Accelerometers are growing in popularity as an objective way to measure physical activity, especially in healthy populations [13], and have been validated using calorimetry and doubly labelled water methods [14]. Actical accelerometers are small, unobtrusive and comfortable and measure acceleration of the limb to which they are attached by detecting low-frequency (0.5–3.2 Hz) forces (0.05–2.0 *g*) [13]. Acceleration is thought to be directly proportional to muscle forces generated, and therefore to energy expenditure [9]. This theory along with an inbuilt algorithm allows for the conversion of energy expenditure into activity counts, which are generated every minute. These counts can be classified into thresholds, indicating sedentary, light, moderate or vigorous intensity levels [9]. Accelerometers have advantages over self-reported measures, such as being able to objectively track intensity, duration and frequency of an activity without relying on patient recall [15]. Acticals in particular can detect varying levels of activity and movement in multiple planes [10], making them potentially ideal for measuring physical activity in patients with RA, who are generally sedentary and where most movement is functional and of low frequency and intensity, and therefore unlikely to be reported accurately using self-report measures.

Accelerometry has already been used to quantify physical activity levels in other rheumatic diseases, such as OA [16], and to study knee biomechanics in SpA and RA patients [17]. The aims of this study were to assess the potential clinical utility of accelerometry in quantifying habitual physical activity levels and patterns in a group of patients with RA by assessing whether varying levels of habitual physical activity are associated with disease activity and HRQoL and to compare their physical activity levels with those of a healthy group of control participants.

Participants and methods

Participants

Fifty female patients fulfilling the 1987 ACR classification criteria for RA [18] with a mean age of 48 (13) years were recruited from the Chris Hani Baragwanath Rheumatology Clinic in Soweto, South Africa (RA group). Participants were excluded if they had any co-morbidities, including cardiac, muscle or neurological disorders, that could potentially impact on physical activity, were using any assistive walking devices or were pregnant. The RA group was compared with 22 control participants (control group) who were matched for mean BMI {calculated as weight (kg)/[height (m)]^2}, race, and sex and were recruited from the same geographical living area as the RA patients so as to closely match the two groups for socioeconomic circumstances. Ethics approval was obtained from the human research ethics committee of the University of the Witwatersrand (M110430 and M110236) and complies with the Helsinki Declaration. All participants signed written informed consent and were free to withdraw from the study at any time.

Outcome assessments

Physical activity

Actical accelerometers (Respironics Inc., Murrysville, PA, USA) were worn on a velcro belt on the hip of the dominant leg during the day for 2 consecutive weeks (the Actical device has been shown to be most accurate when placed on the part of the body where the motion occurs, and studies have shown the hip to be the only place able to predict free living, habitual activities at all intensity levels [13]). Acticals were removed only when the participants were bathing/showering or participating in any water-based activities. Actical data were recorded in 1 min epochs and data were reduced by removing only full days of non-wear time (as observed in the counts or as reported by the participants), as well as sleeping time as reported by participants. The remaining data (which included daily activities as well as rest periods throughout the day) are referred to as the wear period, which was calculated in a similar manner to that described by Semanik *et al.* in 2010 [5]. Data for the wear period were divided into thresholds, namely sedentary, light, moderate or vigorous activity according to the activity counts recorded and the inbuilt algorithm calculated by the Actical software (Respironics Inc., Murrysville, PA, USA). Since the participants were found to be extremely sedentary, these data were then expressed as percentage of time spent in sedentary activities on average per day as recommended by Pate *et al.* in 2008 [19]. The 95th percentile of the activity counts recorded over the period for each participant was also noted in order to eliminate any outliers in maximal activity counts. Activity counts for each participant were also divided into time intervals throughout the day in order to assess daily

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habitual physical activity patterns in RA patients (early morning: 6 am–9 am, late morning: 9 am–12 pm, afternoon: 12 pm–3 pm, late afternoon: 3 pm–6 pm and evening: 6 pm–9 pm), and the average activity counts in each time interval throughout the day were compared between the control group and patients with RA. Participants also completed a physical activity questionnaire after the 2 weeks stating the type of activities undertaken over the study period, which was used to assess any water-based activities that were not recorded by the Actical.

Actical calibration

It has been recommended that accelerometers be calibrated according to the types of activities they would be recording [20]. All Acticals were calibrated for light ambulatory activity typical of patients with RA by being worn by the same person on the hip of the dominant leg while walking on a treadmill (StarTrac S, Toronto, Canada) for 5 min at a standard speed (5 km/h) and with no inclination. The marker button on the Actical was pressed at the start and end of the 5-min period and data were recorded as average activity counts per minute over the period. The average activity counts recorded for each person over the 2-week period was then divided by the calibrated value that was determined for the respective Actical that the participant wore and this new value was used to classify the participants into more physically active and less physically active groups.

Functional ability, HRQoL and RA disease activity

Before being fitted with an Actical, RA patients completed the Short Form-36 (SF-36) questionnaire, a general assessment of HRQoL comprising of eight categories of health, namely physical function, role physical (the role that health plays on physical function), body pain, general health, vitality, social functioning, role emotional (the role that health plays on emotional function), mental health and reported health, all of which are separated into either composite physical health or composite mental health, and combined to give a total SF-36 score where a higher score indicates a better outcome [21]. RA patients also completed a patient global assessment score (PGA) and a modified Health Assessment Questionnaire (HAQ-DI) [22], which is a well-validated RA-specific assessment of functional capacity where the total score ranges from the best possible result (score of 0) to the worst possible result (score of 3). Patients were all assessed by the same physician (B.H.) before commencing the study with a tender joint count (TJC), swollen joint count (SJC) and physician global assessment (MDGA). These, in combination with the CRP concentration in mg/dl and PGA, were used to calculate the composite Simplified Disease Activity Index (SDAI), with cut-offs of <11, >11 and <26 and >26 for low, moderate and severe disease activity, respectively [21].

Statistical analysis

Unpaired students *t*-tests were used to compare all continuous variables between groups. Pearson's and Spearman's correlations (for parametric and non-parametric data, respectively) were used to determine correlations between the objective physical activity counts (which were first log-transformed to normalize the data) and subjective questionnaire data as well as disease activity scores within the RA group. A one-way ANOVA was used to assess differences between average activity counts within each category of SDAI. HAQ-DI scores were adjusted for age, as well as disease duration in order to eliminate any confounding variables, and this adjusted mean was correlated with activity counts. The RA group was divided into a more physically active group and a less physically active group according to the median average activity count value for all the patients over the 2-week period in order to assess the SF-36 scores using unpaired Student's *t*-tests to compare the two groups. All statistical analyses were done using STATISTICA v10.0 (Tulsa, OK) and a *P*-value < 0.05 was considered significant. All data are reported as mean (S.D.).

Results

The characteristics of the groups are summarized in Table 1. There were no differences between the two groups for any of the variables measured except for age, which was significantly greater in the RA group than in the control group ($P = 0.018$). The mean BMI of both the RA and the control groups was greater than 30, categorizing participants as obese according to the WHO [23].

The percentage wear time during the day [15 (3) hour awake per day] spent in sedentary activity is shown in Fig. 1. Overall, RA patients spent a significantly greater percentage of their day in sedentary activity than the control participants [71% (11%) *vs* 62% (11%), $P = 0.002$], and had a significantly lower value than the control group for the 95th percentile of activity counts recorded [22612 (12255) counts *vs* 37091 (17650) counts, $P < 0.001$]. None of the participants took part in any water-based activities.

We assessed how time of day affects physical activity by examining three hourly intervals throughout the day (morning, late morning, midday, afternoon and evening). The average activity counts per three hourly intervals were significantly lower in the RA group compared with the control group for each time category [except for in the evening where there was no difference between the two groups ($P = 0.589$)], as shown in Fig. 2. These differences between the RA patients and controls was greater in the morning ($P < 0.001$) and the afternoon ($P < 0.001$) than in the late morning ($P = 0.033$) and at midday ($P = 0.037$).

Table 2 shows a correlation matrix between physical activity counts and various outcome measures. Activity counts were negatively correlated with age, BMI and disease duration and positively correlated with the composite physical health score of the SF-36. There was no correlation between SDAI and physical activity, and there was no difference in the average activity counts of participants who fell into the respective disease classification categories of SDAI ($P = 0.976$). RA participants had a moderate functional disability according to the HAQ-DI scores shown in Table 1 [22]. HAQ-DI, when corrected for

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TABLE 1 Characteristics of the RA participants and control participants

	RA group ($n = 50$)	Control group ($n = 22$)	P value
Age, years	48 (13)	41 (8)	0.018*
Height, m	1.58 (0.05)	1.59 (0.11)	0.586
Weight, kg	80.20 (24.67)	77.30 (15.61)	0.615
BMI, kg/m^2	32 (9)	31 (8)	0.639
Disease duration, months	99 (77)		
SDAI	16 (11)		
TJC	4 (5)		
SJC	3 (3)		
Physician global assessment	4 (3)		
Patient global assessment	5 (3)		
CRP, mg/dl	19.68 (31.26)		
HAQ index	1.3 (0.9)		

All values are mean (S.D.). *$P < 0.05$.

FIG. 1 Histogram showing the percentage of time spent in sedentary activity between the RA group (black bars) and the control group (white bars).

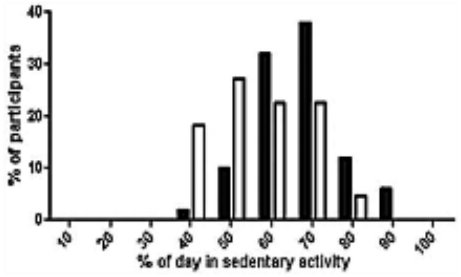
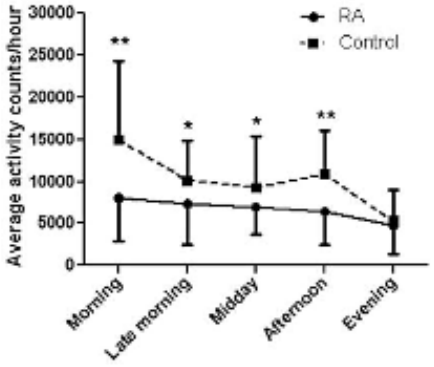


FIG. 2 Average activity counts per 3-h interval for the RA group (solid line) and control group (hatched line) throughout the day.



Morning was calculated from 6 am to 9 am, late morning from 9 am to12 pm, midday from 12 pm to 3 pm, afternoon from 3 pm to 6 pm and evening from 6 pm to 9 pm. The control group had significantly higher activity counts than the RA group at all time points except for in the evening. *$P < 0.050$, **$P < 0.001$.

age and disease duration, was negatively correlated with physical activity ($r^2 = 0.117$, $P = 0.026$) in the group of RA patients as shown in Fig. 3.

There was a wide range of activity counts within the RA group. In order to assess whether SF-36 scores would be different between a more active RA group and a less active RA group, we arbitrarily divided the RA group into a more physically active group and a less physically active group based on the median physical activity count of 1885. The results for the SF-36 between the RA patients (once divided into a more physically active and a less physically active group) are shown in Fig. 4. Both groups scored poorly (<66), yet the more physically active group scored higher than the less physically active group on every component of the SF-36, and significantly higher for the vitality component [54 (17) *vs* 45 (17), $P = 0.04$], the composite mental health component [53 (17) *vs* 44 (16), $P = 0.05$], the composite physical health component [47(19) *vs* 37(18), $P = 0.05$], and the total SF-36 score [49 (18) *vs* 39 (17), $P = 0.03$]. The vitality component of the SF-36 was positively correlated with physical activity in the RA patients, and the total SF-36 score trended towards a significant positive correlation with physical activity ($r = 0.269$, $P = 0.097$) as shown in Table 2.

Discussion

We have used accelerometry to quantify habitual physical activity in patients with RA compared with healthy, matched controls. Our data support the clinical utility of accelerometry as an outcome measure of habitual physical activity in patients with RA as demonstrated by its association with SF-36 and HAQ-DI. In addition, we

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TABLE 2 Correlation matrix comparing various outcomes with average activity counts per day (when log-transformed for normality) within the RA group ($n = 50$)

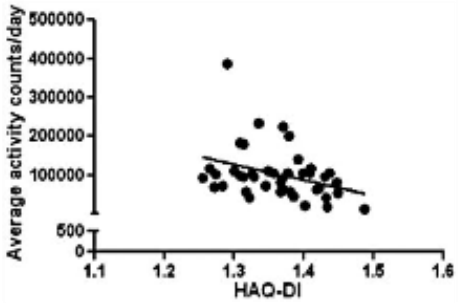
	Spearman *R* or *r* value	*P* value
Age	−0.441	0.005*
BMI	−0.361	0.023*
SDAI	0.172	0.295
ESR	−0.133	0.419
CRP	−0.028	0.852
Disease duration	−0.406	0.010*
SF-36		
Total	0.269	0.097
Composite mental health	0.189	0.247
Composite physical health	0.326	0.043*
Physical function	0.289	0.074
Role physical	0.173	0.235
Body pain	0.221	0.177
General health	0.207	0.207
Vitality	0.187	0.255
Social functioning	0.117	0.477
Role emotional	0.100	0.492
Mental health	0.031	0.853
Reported health	0.061	0.712

Correlations were Spearman's correlations for non-parametric data and Pearson's correlations for parametric data as applicable. *$P < 0.05$.

have shown quantifiable differences in physical activity levels over the course of a day between a group of patients with RA and healthy, matched controls. Patients with RA in the present study were more sedentary and less habitually physically active than healthy, matched controls. An average American adult spends 60% of their day in sedentary activities [24]. Our control group spent a similar percentage of their day in sedentary activities, yet our RA group spent almost 2 h more each day in sedentary activities than their healthy matched controls.

Daily habitual physical activity patterns for patients with RA were markedly different to that of healthy controls. RA patients were significantly more sedentary than control participants throughout the day except for in the evening, when the two groups converged to a similar average level of activity. Interestingly, the control participants had two peaks in habitual physical activity levels that were not present in the RA group. These occurred in the early morning and late afternoon. The absence of these peaks in activity levels in the patients with RA are likely to be related to two known symptoms of the RA disease, namely morning stiffness of the joints [25] and fatigue, which tends to peak in the afternoon [26]. Fatigue is an important barrier to physical activity in patients with RA and was shown to be negatively associated with subjectively measured physical activity levels in patients with RA [12]. The ability of the accelerometer to detect the presence of these symptoms, as well as to differentiate between the two groups through measurement of physical activity, makes it a promising tool in the measurement of RA disease outcomes.

FIG. 3 Correlation between the average activity counts per day in the patients with RA and HAQ-DI adjusted for age and disease duration.



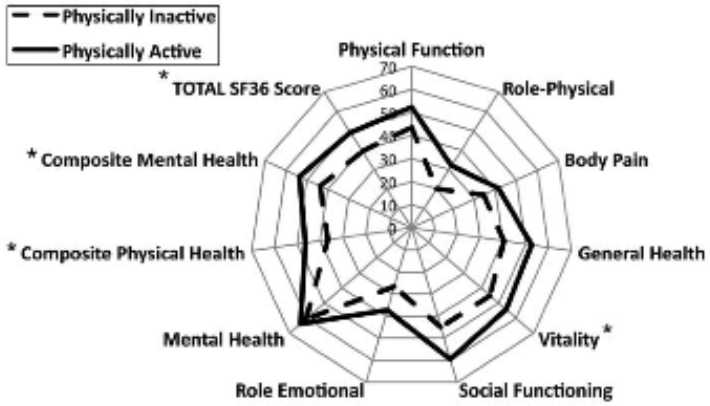
$r = 0.343$, $P = 0.026$.

Similarly to Sokka *et al.*, we have reported decreased functional ability in patients with RA in association with decreased physical activity levels, but have extended and further unpacked this finding with the use of an objective measure of physical activity. The clinical utility of accelerometry devices could minimize the difficulties associated with language and questionnaire limitations. Functional capacity (as assessed by the HAQ-DI) was shown in the current study to be negatively correlated with objectively measured physical activity in patients with RA. Higher levels of habitual physically activity may have a protective role on functional disability in patients with RA. de Jong *et al.* [27] in 2003 found HAQ scores to decrease (although not significantly) in a group of patients with RA who underwent dynamic exercise training for 2 years. Also, Walker *et al.* [28] in 1999 found HAQ scores to be negatively correlated with ambulatory activity in patients with RA as measured by a Numact activity monitor, which only assesses energy expenditure, calculated from number and vigour of steps taken. Henchoz *et al.* [12] in 2012 found that HAQ was not associated with physical activity, yet their study did not assess physical activity objectively. Despite this, all disease-related scores were found to be significantly poorer in sedentary compared with physically active patients. We show an association between increased levels of objectively assessed habitual physical activity (using a calibrated activity monitor capable of quantifying intensity and frequency of activity within certain thresholds) and functional ability in patients with RA, supporting the utility of the accelerometer as a complementary outcome measure for RA.

Within our RA group, more physically active patients scored better in almost every domain of SF-36 than less physically active patients, and therefore patients with greater habitual physical activity levels reported feeling better than less physically active patients. This is in

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FIG. 4 Spydergram showing the components of the SF-36 questionnaire for the RA group.



RA group divided according to the median activity count value of the whole group into a more physically active group (solid line) and a less physically active group (hatched line). The more physically active group scored significantly higher than the less physically active group for vitality ($P = 0.034$), overall physical health ($P = 0.05$), overall mental health ($P = 0.05$) and total SF-36 score ($P = 0.03$).

keeping with a previous study that showed exercise to improve the sense of well-being in a group of females with RA of a similar age range to our participants [4]. These findings imply that, although not necessarily having an effect on disease activity, higher levels of habitual, ambulatory physical activity are associated with improved quality of life and sense of well-being, potentially making the disease easier to cope with.

Despite our RA group not nearly meeting the current recommended guidelines for physical activity (30 min of moderate to vigorous activity every day of the week [19]), those that simply had higher habitual physical activity level fared better on assessments of functional status and well-being despite the lack of association with disease activity. It is important to develop healthy, feasible guidelines for patients with chronic limitations of movement, potentially focusing more on increasing light activity and decreasing sedentary activity as an adjunct to increasing moderate to vigorous activity where possible. Patients with RA may need frequent rest breaks depending on the severity of their disease [5], and it might be necessary to develop different Actical cut-off points for activity levels in people with chronic pain conditions in order to allow for the increased periods of non-movement time to be considered. The Actical was able to quantify ambulatory habitual physical activity levels in this group of patients with RA, which is the first step in developing guidelines for this population.

SDAI was not significantly correlated with physical activity. We attribute the absence of a relationship between physical activity and SDAI to the fact that SDAI is comprised largely of tender and swollen joint counts, 26 out of 28 of which are upper limb joints. An activity monitor placed on the hip would measure only ambulatory, lower limb activity and not upper limb activity. It may be necessary to look at the associations between physical activity and deformity of the joints (especially lower limb joints) as assessed by an X-ray or a clinical measure of joint deformity such as the RA articular damage score (RAAD score) [29].

The limitations of this study include the cross-sectional design, which limits the causality conclusions we can draw. While increased habitual physical activity levels were associated with improved well-being and better functional status, it is not clear if this is the cause or the effect. Also we focused only on females, and these results cannot necessarily be extrapolated to males, although the incidence of RA is much higher in females [26]. We also excluded patients who were using assistive walking devices, which limits the extrapolations we can make to RA patients needing to make use of such devices. Lastly, we did not manage to successfully match the ages of the control group with the RA group, and although this was controlled for in the analysis, it is still a limitation to the study.

In conclusion, RA patients have decreased habitual physical activity levels in comparison with healthy, matched controls. The daily physical activity patterns of the patients with RA do not show the same bimodal peaks seen in healthy control participants and are likely to be related to periods of morning stiffness and fatigue. The activity counts recorded by the Actical accelerometer correlate well with the HAQ-DI, giving the Actical construct validity as a novel outcome measure in RA. Furthermore, patients with higher physical activity levels scored better with regards to the SF-36 in both physical and mental domains. A longitudinal study is needed to assess the

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responsiveness of physical activity to changes in disease activity.

Rheumatology key messages

- Actigraphy counts are negatively correlated with HAQ scores in patients with RA.
- More physically active RA patients scored better than less physically active patients on many components of SF-36.
- RA patients demonstrated quantifiable bimodal decreases in daily physical activity in the morning and late afternoon.

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Disclosure statement: The authors have declared no conflicts of interest.

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Appendix 12 – Study 2

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RHEUMATOLOGY 53

Concise report

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Changes in physical activity measured by accelerometry following initiation of DMARD therapy in rheumatoid arthritis

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Abstract

Objective. The aim of this study was to assess changes in habitual physical activity levels in response to DMARD therapy in RA patients.

Methods. Eighteen drug-naive RA patients were prospectively assessed at baseline and following 3 months of DMARD therapy for habitual physical activity by accelerometry, disease activity using the clinical disease activity index (CDAI) and functional disability using the modified HAQ (mHAQ). Baseline physical activity was also compared with an equal number of healthy control participants matched for age, sex and BMI.

Results. Following 3 months of DMARD therapy, in parallel with significant improvements in CDAI scores ($P < 0.001$) and HAQ scores ($P < 0.001$), accelerometry measures in the RA cohort showed that the average activity counts in sedentary thresholds decreased ($P = 0.012$), while average activity counts within higher-intensity thresholds increased ($P = 0.039$). Multiple regression analysis showed that the change in moderate activity was associated with a decrease in CRP ($\beta = -0.922$, $P = 0.026$) while the decrease in sedentary activity and increase in moderate activity were associated with decreased morning stiffness of the joints ($\beta = 0.694$, $P = 0.035$ and $\beta = -0.927$, $P = 0.024$, respectively). At baseline, RA patients were less physically active than control participants in the morning ($P = 0.048$) and in the late afternoon ($P = 0.016$), but these diurnal differences were no longer significant after the DMARD intervention.

Conclusion. These findings suggest that accelerometry may potentially be a viable objective method of assessing changes in physical disability in response to various disease-modifying drugs.

Key words: physical activity, DMARD therapy, accelerometry, rheumatoid arthritis.

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CLINICAL SCIENCE

Introduction

Physical disability in RA is a consequence of a combination of active synovitis, joint deformities and chronic pain [1]. This results in most patients adopting a more sedentary lifestyle. Measures of functional disability in RA, although shown to correlate well with measures of disease activity and joint damage [2, 3], are subjective, and thus far no objective measures of physical functionality for patients with RA have been routinely included in clinical practice or in clinical trials.

Accelerometry has been used previously as an objective measure of physical activity in RA [4–6]. However, there is a paucity of knowledge regarding its use in RA as a measure of habitual physical activity levels such as locomotion, leisure activities and conscious exercising. Moreover, it is unclear whether RA patients would become more habitually physically active with better symptom control or to what extent a change in disease activity impacts on habitual physical activity levels.

We previously found, in a cross-sectional study, that physical activity levels measured by the Actical accelerometer were reduced in RA patients compared with

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healthy controls [7]. The present longitudinal study used the same method to measure changes in habitual physical activity levels in newly diagnosed RA patients after being treated with DMARDs to control disease activity [8] and to investigate the relationship of changes in habitual physical activity levels with disease activity.

Patients and methods

Eighteen South African female patients with newly diagnosed DMARD-naive RA, fulfilling the 1987 ACR classification for RA [9], were recruited for the study. Exclusion criteria were co-morbidities that could affect physical activity levels, such as history of a previous stroke, cardiac disease, severe disability requiring the use of assistive walking devices or pregnancy. The RA group was compared with a control group of 18 healthy participants, matched for ethnicity, age, sex, BMI and geographical area. Ethical approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (M110430 and M110236) and all patients gave written informed consent to participate in the study.

Patients were assessed at baseline and at a 3 month follow-up visit after initiating DMARD therapy (MTX 15 mg/week at baseline, increased monthly by 5 mg/week, combined with prednisone 7.5 mg/day until low disease activity [clinical disease activity index (CDAI) < 11] was achieved. Assessments at the two visits included the duration of early morning stiffness (EMS) of the joints, CDAI (done by B.H.) [10], height, weight, CRP and completion of the modified HAQ (mHAQ) [11] and 36-item Short Form (SF-36) [12] by the patients.

Actical measurements

Participants were fitted at baseline and the follow-up visit with an Actical accelerometer (Respironics, Murrysville, PA, USA). The instrument was worn on a Velcro belt on the hip of the dominant leg for 2 consecutive weeks, removed only for bathing or showering or any other water-based activities. Each patient wore the same Actical instrument at baseline and follow-up visits so as to avoid any interdevice differences in data recording. DMARDs and oral prednisone were withheld during the initial 2 weeks following enrolment in the study to obtain baseline Actical readings. In exceptionally severe cases, intra-articular steroid injections (methylprednisolone acetate) were administered only if the affected joint was on the upper limb so as not to affect the Actical readings. Control participants were fitted with an Actical on the dominant hip for 2 weeks at baseline only.

Actical data were recorded in 1 min epochs, removing full days of non-wear (defined as a full day of consistent zero activity counts). The remaining data are referred to as the wear period [13]. Data for the wear period were divided into thresholds—sedentary, light, moderate or vigorous activity—according to the activity counts recorded and the built-in algorithm calculated by the Actical software. Activity data were represented as average activity counts during the awake period per hour over the 2 week period [the mean awake day period was 16.0 hours (S.D. 2.3) and 15.7 hours (1.3) at baseline and follow-up, respectively, $P = 0.614$]. Data were then expressed as average activity counts within each threshold per day as recommended previously [14]. The 95th percentile of the activity counts recorded over the period for each participant was also noted in order to eliminate any outliers in maximal activity counts.

Statistical analysis

The paired Student's *t*-tests and Wilcoxon matched-pairs tests were used to compare changes from baseline in continuous variables for parametric data and non-parametric data, respectively. The Spearman's correlation test was applied to determine correlations between physical activity data and clinical data. A backwards stepwise multiple regression was run to determine predictors of various changes in disease activity outcomes. All statistical analyses were done using STATISTICA version 10.0 (StatSoft, Tulsa, OK, USA). All data are presented as mean (S.D.). *P*-values < 0.05 were considered significant.

Results

RA group compared with control group at baseline

There were no significant differences between the RA group and control group with respect to age [50 years (14) *vs* 44 (7), $P = 0.103$], height [1.59 m (0.06) *vs* 1.60 (0.11), $P = 0.629$] and weight [76 kg (22) *vs* 73 (11), $P = 0.677$]. The mean BMI was in the obese range for both groups [30 kg/m^2 (8) *vs* 29 (5), $P = 0.613$]. The symptom duration in the RA group at baseline was 43 (55) months.

Disease and physical activity changes in the RA group at the 3-month follow-up visit

Significant improvements were observed in the duration of EMS [101 min (64) to 46 (56), $P = 0.048$], CDAI [41 (11) to 14 (8), $P < 0.001$], mHAQ scores [1.94 (0.87) to 0.98 (0.76), $P < 0.001$], and in the SF-36 domains of body pain ($P < 0.001$), vitality ($P = 0.002$), role emotional ($P = 0.047$), physical health ($P = 0.003$) and mental health ($P = 0.038$).

As shown in Table 1, there were significant decreases in sedentary activity measures and significant increases in light activity measures at the follow-up visit when compared with baseline. The average activity counts in sedentary activity at the follow-up decreased significantly, and the same was true for the activity counts at the 95th percentile within sedentary activities. There was a trend towards increased average activity counts in light activity, while the activity counts in the 95th percentile of light activity increased significantly. No significant changes were noted in moderate or vigorous activity thresholds.

On dividing the daily activity counts into 3-hourly intervals (Fig. 1), no significant differences were found between the average activity counts spent in each time period at baseline and at the 3 month follow-up visits within the RA group. However, compared with the control group, the RA group was significantly less active in the morning ($P = 0.048$) and the late afternoon ($P = 0.016$) at

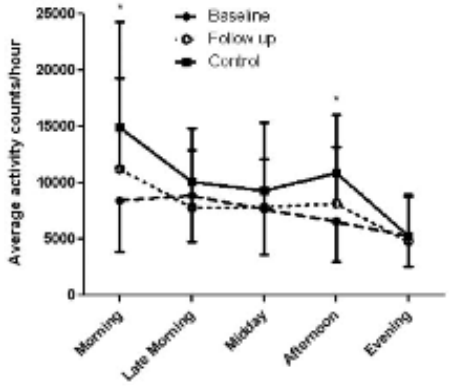
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TABLE 1 Physical activity measures at baseline and 3 month follow-up visits in the RA group

	Baseline, mean (S.D.) ($n = 18$)	Follow-up, mean (S.D.) ($n = 18$)	P-value
Average activity, counts/day	110 908 (42 942)	112 502 (61 190)	0.286
Sedentary activity			
Average counts	428 (124)	354 (158)	0.012*
95th percentile counts	995 (283)	837 (253)	0.004*
Light activity			
Average counts	1208 (665)	1496 (810)	0.094
95th percentile counts	3461 (1453)	4451 (2057)	0.039*
Moderate activity			
Average counts	5431 (3062)	5615 (4266)	0.983
95th percentile counts	22 087 (12 292)	24 271 (16 074)	0.948
Vigorous activity			
Average counts	50 (135)	44 (120)	0.612

*Activity data significantly improved at follow-up as compared with baseline ($P < 0.05$).

FIG. 1 Average activity counts spent in 3-hourly intervals throughout the day between RA patients and controls



$P < 0.05$ between the RA patients at baseline and the control group.

baseline, but these differences were no longer evident between the groups at the follow-up visit.

The decrease in CRP levels correlated with an increase in moderate activity ($r = -0.577$, $P = 0.039$), improvement in mHAQ scores correlated with an increase in vigorous activity ($r = -0.536$, $P = 0.022$) and improvement in the vitality score of the SF-36 correlated with an increase in the average daily activity count ($r = 0.646$, $P = 0.005$). On multivariate regression analysis, the correlation between the decrease in CRP levels and increase in moderate activity remained significant ($\beta = -0.922$, $P = 0.026$), and the decrease in sedentary activity and increase in moderate activity correlated with decreased EMS ($\beta = 0.694$, $P = 0.035$ and $\beta = -0.927$, $P = 0.024$, respectively). An unexpected finding was the significant increase in the mean height of RA patients from baseline to the follow-up visit [1.59 (0.06) to 1.60 (0.06), $P = 0.021$], which was also correlated with a decline in the tender knee joint count ($r = 0.528$, $P = 0.043$).

Discussion

Our findings show that the Actical accelerometer was sensitive in detecting changes in habitual physical activity in patients with established RA following treatment with DMARDs. *Pari passu* with the improvement in traditional measures of disease activity, functional ability and health-related quality of life following initiation of DMARD therapy, there was significant improvement in accelerometry measures of habitual physical activity. There was a significant reallocation of activity counts from participation in sedentary activity (activities requiring minimal energy expenditure over and above resting metabolic rate, such as lying down and sitting) to increased participation in light activity (activities such as standing up and light walking). The decrease in mean activity counts in the sedentary activity threshold in conjunction with the increase in mean activity counts within the light activity threshold are indicative of patients breaking up their sedentary activities with light activities more frequently than before the DMARD therapy intervention.

Our findings also suggest that components of the Actical accelerometer measurements correlate well with validated outcome measures of RA disease. Increases in moderate and vigorous activities correlated with a decrease in CRP levels and improvement in mHAQ scores, respectively. The diurnal variation in habitual activity levels (with significantly lower activity levels observed at baseline in the early morning and late afternoon in the RA group compared with the control group) are likely to be related to two common symptoms of active RA, namely EMS and late afternoon fatigue. These differences were no longer significant at the follow-up visit. Moreover, the improvement in EMS correlated significantly with the overall increase in moderate activity

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counts. Although we did not directly quantify afternoon fatigue levels, the vitality component of the SF-36 has been shown to be a relevant measure of overall fatigue in RA [15]. The improvement in vitality scores correlated significantly with the increase in the average daily activity counts.

One of the limitations of the Actical measurements was that, by virtue of being placed over the hip, the device essentially measures only lower limb movement, while inflammation and deformities in upper limb joints contribute substantially to the overall physical disability in RA. A further limitation is that we excluded patients with severe disability (i.e. requiring assistive devices) and that participants included were mostly obese, limiting extrapolations to the general RA populace. The lack of a follow-up assessment of control participants limits the conclusions that can be drawn with regards to natural variations in physical activity that may occur over time.

Notwithstanding these limitations, our findings suggest that accelerometry may potentially be a viable objective method of assessing changes in physical disability in response to various disease-modifying drugs. Future studies should be aimed at including a larger sample size and patients with more severe disability, allowing a longer study duration and including an exercise intervention programme where patients are encouraged to increase physical activity.

Rheumatology key messages

- The Actical detects changes in physical activity in RA patients following treatment with DMARDs.
- Improvements in RA disease activity are associated with increased habitual physical activity levels.
- Diurnal decreases in physical activity levels are normalized following DMARD therapy in patients with RA.

Acknowledgements

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Appendix 13 – Protocol Paper

(Under review at BMC Musculoskeletal disorders)

A three month controlled intervention of intermittent whole body vibration designed to improve functional ability and attenuate bone loss in patients with rheumatoid arthritis

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Key Words:

Rheumatoid arthritis

Whole body vibration

Functional ability

Bone mineral density

Physical activity levels

Abstract:

Background: Rheumatoid arthritis (RA) is a chronic autoimmune condition that results in pain and disability. Patients with RA have a decreased functional ability and are forced into a sedentary lifestyle and. As such, these patients often become predisposed to poor bone health. Patients with RA may also experience a decreased health related quality of life (HRQoL) due to their disease. Whole body vibration (WBV) is a form of exercise that stimulates bone loading through forced oscillation. WBV has also been shown to decrease pain and fatigue in other rheumatic diseases, as well as to increase muscle strength. This paper reports on the development of a semi randomised controlled clinical trial to assess the impact of a WBV intervention aiming to iprove functional ability, attenuate bone loss, and improve habitual physical activity levels in patients with RA. **Methods and Design:** This study is a semi randomised, controlled trial consisting of a cohort of patients with established RA assigned to either a WBV group or a CON (control) group. Patients in the WBV group will undergo three months of twice weekly intermittent WBV sessions, while the CON group will receive standard care and continue with normal daily activities. All patients will be assessed at baseline, following the three month intervention, and six months post intervention. Main outcomes will be an improvement in functional ability as assessed by the HAQ. Secondary outcomes are attenuation of loss of bone mineral density (BMD) at the hip and changes in RA disease activity, HRQoL, habitual physical activity levels and body composition.

Discussion: This study will provide important information regarding the effects of WBV on functional ability and BMD in patients with RA, as well as novel data regarding the potential changes in objective habitual physical activity patterns that may occur following the intervention. The sustainability of the intervention will also be assessed. **TRN:** PACTR201405000823418 (19/05/2014).

Introduction:

Rheumatoid Arthritis (RA) is the most common autoimmune disease. RA causes joint swelling, tenderness and destruction of the synovial joints. It is a chronic condition resulting in pain, severe disability and decreased functional ability (1). RA occurs in 1% of people worldwide, with the prevalence being two times higher in women than in men (2).

People living with RA have decreased functional ability. The health assessment questionnaire (HAQ), which is a disease specific measure of functional ability in RA, is one of the most increasingly and widely used outcome measures for RA (3). A large qualitative study conducted in female patients with RA found that patients report pain and decreased functional ability as having the most widespread effect on their daily lives (4). Inability to perform normal daily activities not only decreases quality of life, but also further perpetuates a sedentary lifestyle in these patients. Certain exercise interventions conducted on patients with RA have managed to significantly improve functional ability as assessed by the HAQ through increasing participation in regular physical activity (5).

People living with RA are predisposed to the development of osteoporosis. Patients with RA have been shown to have a lower bone mineral density (BMD) (specifically at the hip and spine, but also for whole body) than age matched controls, as well as an increased fracture risk specifically at the hip and spine (6). The lower BMD (and increased incidence of osteoporosis) may be as a result of the presence of circulating inflammatory cytokines inherent to the disease, the decreased mobility of these patients, resulting in a sedentary lifestyle, or due to certain medications taken to treat the disease such as corticosteroids and methotrexate.

Osteoporosis in RA can be generalised, (affecting the axial skeleton such as the hip and lumbar spine), or peri-articular (affecting local areas of inflammation such as the hand joints) in nature. Studies have shown that the majority of bone density loss in RA occurs in the first six months of disease (7). Furthermore, patients with higher RA disease activity have been shown to exhibit a greater loss in BMD, as well as higher indices of bone metabolism compared to those with lower disease activity. Levels of mobility and functional ability have also been correlated with BMD; as have age, stature, and sex independently of RA disease (8), (9).

People with RA spend large amounts of time in sedentary behaviours. Bone loss in RA is amplified by the decreased mobility and high levels of sedentary behaviour present in these patients (10). Wolff's law, states that the skeleton transforms it's mass and morphology according to individual activity levels and forces placed upon the bone (11). Furthermore, Frost's mechanostat theory states that each bone has a specific strain threshold, and that in order for that bone to be remodeled, the minimum effective strain must be placed upon it (12). A sedentary individual does not place sufficient strain on the skeleton, and bones are thus remodelled in a direction that promotes bone loss. Patients with RA are therefore at increased risk of osteoporosis due to inflammatory processes inherent to their disease; as well as the consequent effect of a sedentary lifestyle (13). Bone mass in RA can be modified using treatments designed to increase bone mass (such as bisphosphonates, Vitamin D and Calcium), treatments to decrease RA disease activity, or by increasing physical activity sufficiently in order to increase bone loading and remodeling. Patients with RA, however, are known to be more sedentary than their healthy counterparts (10).This sedentary lifestyle is worsened by the joint and muscle damage occurring during severe disease, which results in pain, functional disability and musclular atrophy (14), further decreasing habitual physical activity. Moreover, research has shown that exercises aimed at increasing BMD should be dynamic- comprised of short and vigorous bouts of high impact exercise incorporating rest periods (15). This type of exercise is usually not feasible in patients with a chronic, disabling pain condition such as RA.

Furthermore, RA patients have long been shown to have a decreased health related quality of life (HRQoL) in comparison to the general population (16), which is largely due to the presence of the chronic pain they experience (ref). HRQoL is a relevant measure of disease activity according to the World Health Organisation (17), and studies have shown that "feeling well" is an important patient outcome, along with management of pain, sleep, fatigue, emotional- and physical wellbeing (16). It is thus important to try to limit the amount of pain experienced by patients with RA in order to improve their quality of life and increase their physical activity. Physical activity in patients with RA has been shown to improve sense of wellbeing, decrease morning stiffness, improve sleep patterns, and decrease swollen joint counts over time (18), as well as reducing pain and improving functional ability in these patients (19). These benefits are achieved through mobilization of joints and increasing muscle strength.

Physical activity, as a functional assessment of quality of life can be difficult to assess. Questionnaires and recall diaries are commonly used but are subjective (20), and it is often difficult for patients to recall their activity levels accurately, especially for light to moderate activities (21). Accuracy in these subjective measures also relies on patient fluency in the English language and compliance, and they cannot necessarily be used in all population groups. Accelerometers are growing in popularity as an objective way to measure physical activity, especially in healthy populations (22).

Accelerometers are small, unobtrusive and comfortable, and measure acceleration of the limb to which they are attached by detecting low frequency (0.5-3.2 Hz) gravitational forces (0.05-2.0g) (22). Acceleration is directly proportional to muscle forces generated, which is proportional to energy expenditure (21). This theory along with an inbuilt algorithm allows for the conversion of acceleration into activity counts, which are generated every minute (or in specific time intervals as specified by the user). These counts can be classified into thresholds, indicating light, moderate or heavy intensity levels (21). The Actical device has been shown to be most accurate when

placed on the part of the body where the motion occurs, and studies have shown the hip to be the only place able to predict free living activities at all intensity levels, with the wrist and ankle being second and third best respectively (22). Generally, the device needs to be worn for a minimum of ten hours per day in order for that day to be considered valid (23), and at least three valid days of data are required for analysis. Although in many studies 60 continuous minutes of zero activity counts are excluded as non wear time (23); this may not be feasible in an RA population where patients can spend many hours per day being sedentary, therefore continuous zero activity counts may be reflecting extended periods of sedentary time rather than non wear time and thus cannot be excluded.

Acticals have advantages over self-reported measures, such as being able to track intensity, duration and frequency of an activity without relying on patient recall (24). Acticals in particular, can detect varying levels of activity, being able to detect lower level activities and movement in multiple planes (22) and are therefore an ideal tool for measuring physical activity and sedentary behaviour in patients with RA, where most movement is functional and of a low frequency and intensity, and therefore unlikely to be reported accurately using self report measures. Indeed accelerometry has already been used to this effect in other rheumatic diseases (25), as well as in patients with RA (26).

Traditional exercise interventions may not be feasible in a population with RA. Exercise interventions making use of light aerobic activity and strength training, as well as stretching, have been conducted in various cohorts of RA patients with varied results, with most studies showing exercise to improve physical fitness and muscle strength with either no change or improved disease activity outcomes (27), however these interventions do not specifically address the problem of low bone mass in these patients.

Whole body vibration (WBV) is a potential novel exercise intervention for people with RA. WBV therapy is an exercise whereby a mechanical vibration platform produces energy via forced oscillation. The vibratory waves

are then transferred to an individual via propagation through the feet, legs, trunk and finally, the head (28). Studies conducted in postmenopausal women (29), as well as healthy populations (30), and athletes with low BMD (31), have shown WBV therapy to improve BMD, particularly at the hip and spine (32) (33). Although the exact mechanisms whereby WBV therapy increases BMD are unclear, it is likely that there are multiple mechanisms at play. WBV has been shown to activate fluid flow in the caniliculi and lacunae of bone matrix in rats (34), in a manner proportional to loading frequency. This fluid flow creates shear stress on the plasma membrane of osteocytes, bone lining cells, and osteoblasts, which therefore respond accordingly (15). WBV thus activates mechanostransduction in bone and stimulates osteogenesis (34). Furthermore, muscle forces have been shown to exert the greatest osteogenic stimulus on bone, and the generation of these forces through vibration stimulus is likely a contributor to the skeletal adaptations that occur (35). According to Frost's mechanostat theory, vibration stimulus must sufficiently load bones in order to increase deposition.

WBV has already been used as a means to treat osteoporosis in otherwise healthy populations with low BMD (34), older individuals (36), postmenopausal women (29), athletes at risk of osteoporosis (31), as well as in other diseased populations (37) with mainly positive results including (along with increased BMD), increases in muscle strength, improved proprioception and balance, and decreased pain and fatigue levels. Furthermore, WBV therapy has been shown to increase peripheral blood flow (38) as well as cardiovascular performance (30), and could therefore have an effect on cardiovascular health. Trans et al (2009), used WBV in patients with knee osteoarthritis and found 8 weeks of twice weekly vibration training to significantly improve knee strength in these patients, but did not assess BMD (39). Alentorn-Geli et al (2008) used a dynamic and static WBV protocol, twice weekly for 6 weeks in a group of female patients with fibromyalgia (40). Patients in this study were divided into a control group (who underwent no therapy), an exercise group (who underwent standard RA exercise therapy only), and a WBV group (who underwent WBV training on top of the standard exercise therapy. The authors of this study found that the WBV protocol

are then transferred to an individual via propagation through the feet, legs, trunk and finally, the head (28). Studies conducted in postmenopausal women (29), as well as healthy populations (30), and athletes with low BMD (31), have shown WBV therapy to improve BMD, particularly at the hip and spine (32) (33). Although the exact mechanisms whereby WBV therapy increases BMD are unclear, it is likely that there are multiple mechanisms at play. WBV has been shown to activate fluid flow in the caniliculi and lacunae of bone matrix in rats (34), in a manner proportional to loading frequency. This fluid flow creates shear stress on the plasma membrane of osteocytes, bone lining cells, and osteoblasts, which therefore respond accordingly (15). WBV thus activates mechanostransduction in bone and stimulates osteogenesis (34). Furthermore, muscle forces have been shown to exert the greatest osteogenic stimulus on bone, and the generation of these forces through vibration stimulus is likely a contributor to the skeletal adaptations that occur (35). According to Frost's mechanostat theory, vibration stimulus must sufficiently load bones in order to increase deposition.

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significantly improved fatigue scores, as well as pain scores in comparison to the exercise group, or the control group, however no measures of BMD were taken. Certain studies have shown WBV therapy to have no effect on BMD in healthy adults (41), or on fatigue or pain levels, balance, or strength (42).

WBV has not, to our knowledge, been used as an exercise intervention for RA, yet it may be a feasible means to increase functional ability in these patients. Since patients with RA are already at risk for developing osteoporosis, and are therefore at greater risk of fracture; WBV could also potentially be a means to attenuate the progressive loss of BMD observed in patients with RA, without the need for a vigorous exercise programme. With this background in mind, the aims of this study are primarily to determine the effects of a WBV programme on functional ability in patients with established RA in comparison to a control group of patients, as well as to determine any effects WBV therapy may have on BMD, disease activity, physical activity levels, HRQoL, or body composition in these patients.

Methods:

Study Design:

A semi randomised, single blinded, controlled, two-group parallel design in accordance with the 2010 CONSORT guidelines will be used; with patients being allocated to either group in an alternating manner upon enrollment. Patients in the WBV group will begin a WBV therapy intervention programme for a three month period, while those in the CON group will continue to receive standard care for the three month period. All patients will be assessed at three time points, as follows:

Participants:

Participants will be recruited from the Rheumatology Clinic at the Chris Hani Baragwanath Academic Hospital in Soweto, South Africa. Recruitment will include the outpatients attending the clinic at the quarterly check-up via a brief interview following dissemination of study information. Consenting patients will be included if they are older than 18 years, have been diagnosed with RA (according to the 1987 ACR criteria (43)) at least three years previously, are on stable drug therapy (prednisone <10mg/day), and had been for at least three months previously. Patients will be excluded if they are HIV+, are using bisphosphonates or corticosteroids, have any co-morbidities that could potentially impact on physical activity levels, are using assistive walking devices, have previously had hip or knee joint replacement surgery, and if they are pregnant.

Ethical Consideration:

This study complies with the international ethical guidelines for a clinical study. Ethical approval has been obtained from the Human Research Ethics Committee of the University of the Witwatersrand (M130113). Patients will be required to read and sign informed consent, and revocation of consent will not detriment the patients in any way.

Trial Registration:

This study has been registered with the Pan African Clinical Trial Registry and

has the trial number PACTR201405000823418.

Intervention and control:

All vibration training will be performed on standard power plates (DKN XG 5.0, DKN Technology, California, USA) under the supervision of the primary investigator. Vibration training will consist of 24 total sessions (performed twice weekly for 12 weeks); in intermittent bouts of 60 seconds on the plate and 30 seconds off the plate, repeated 10 times (this protocol was designed to stimulate greater osteogenic responses due to the constant stimulus to the mechanoreceptors (31)). Patients will be required to stand on the plates, barefoot and with knees slightly bent, holding firmly to the bars. Vibration plates will be set at a constant frequency of 30Hz and amplitude of 3mm in order to maximize the osteogenic and muscle activation effects of the therapy (31). The CON group will continue to receive standard care for the intervention period, and will be instructed to continue with their normal daily activities for the three month period.

Sample Size:

A sample size calculation (ß=0.10) showed that at a 5% level (using an SD of 0.19) we would require a sample of 8 participants in each group in order to detect a minimum clinically important difference of 0.22 in HAQ score (ref) with a power of 90%.

Outcome measures:

All outcomes will be measured at baseline, and reassessed after the three month intervention. The primary outcome of this study will be an improvement in functional ability as assessed by the HAQ. The secondary outcomes will be an attenuation in loss of BMD at the hip, as well as improvements in subjective pain scores, SF-36, CDAI, and objective habitual physical activity levels (Table 1).

Table 1. Summary of outcome measures and respective methodology

Outcome		**Measurement method**	**Time point (months)**
Primary	Functional Ability	Health Assessment	0,3,6

		Questionnaire	
Secondary	BMD	DXA	0,3,6
	Habitual Physical Activity	Accelerometery (Actical worn on the hip)	0,3,6
	Disease activity	CDAI assessment	0,3,6
	Pain and fatigue	Self reported via Lickert scales	0,3,6
	Body composition and anthropometry	DXA, standard scale, and stadiometer	0,3,6

Primary:

Functional Ability:

Patients will be asked to complete the modified Health Assessment Questionnaire (HAQ) (44), which is a RA specific questionnaire that assesses functional ability by providing a score of functionality between 0 and 3, where 0 indicates good functionality and 3 indicates severe functional disability.

Secondary:

The secondary outcomes of the study are an attenuation in loss of BMD, as well as any improvements in HRQoL, disease activity, habitual physical activity or body composition measurements. These will be assessed as follows:

BMD:

All patients will be assessed, for site specific areal BMD at the left hip, lumbar spine (L1-L4), and whole body using Dual X-Ray Absorbtiometry (DXA). T and Z scores will then be calculated according to reference values. All scans will be performed by the same qualified technician on the same machine (Hologic QDR 4500A, Hologic, Boston, USA). The machine is routinely calibrated, and a phantom spine will be scanned daily to determine coefficients of variation of the machine. The technician will be blinded as to the grouping of participants during the study.

Physical Activity:

At each assessment, patients will be fitted with an Actical (Respironics Inc., Murrysville, PA, USA) accelerometer (for the assessment of habitual physical activity) worn on a Velcro belt on the hip for a one week period. Patients will be instructed to wear the accelerometer all day, and to remove the device only while sleeping, bathing or showering. Patients will then return the accelerometer to the clinic one week later. Actical data are recorded in one minute epochs and data are reduced by removing only full days of non-wear time as observed by a full day of zero activity counts. Sleep time is removed by direct observation of the data, and only the remaining data will be considered as wear time. Ten hours of wear time per day and four days of total wear time will be required for inclusion in the analysis (45). Data will be reported as average activity counts per day, as well as percentage of time spent in sedentary, light, moderate and vigorous activity thresholds, as calculated by the inbuilt algorithim on the Actical software. The number of bouts of activity, as well as the number of breaks in sedentary activity per day will also be reported, the methodology of which has been explained previously (46). Participants will be fitted with the same Actical at each visit in order to minimise inter-device variability. This will allow for the assessment of habitual physical activity patterns before and after the intervention.

Disease Activity:

Patients will be assessed for disease activity using the Compound Disease Activity Index (CDAI) (47) which provides a score comprised of tender joint count (TJC), swollen joint count (SJC), patient global assessment (PGA), and physician global assessment (MGA) calculated as follows:

CDAI=TJC+SJC+PGA+MGA

This score allows for the classification of patients according to the severity of their disease where a score <2.8 indicates remission, a score <10 indicates moderate disease activity, a score <22 indicates moderate disease activity, and a score >22 indicates severe disease activity. The physician will be blinded as to the grouping of participants during assessments.

Pain:

At each assessment, patients will be asked to rate their pain levels over the previous week using a Lickert scale ranging from 0-5, where a score of 0 indicates no pain and a score of 5 indicates unbearable pain.

Fatigue:

At each assessment, patients will be asked to rate their fatigue levels over the previous week using a Lickert scale ranging from 0-5, where a score of 0 indicates not feeling tired at all, and a score of 5 indicates the most tired ever felt.

Anthropometry:

Height and weight will be measured to the nearest cm and kg respectively using a standard stadiometer and scale, with patients barefoot and wearing minimal clothing. Thereafter body mass index (BMI) will be calculated.

Body composition:

Body composition, including fat mass and lean muscle mass will be taken from the DXA scan. Percentage body fat and percentage lean muscle mass will then be calculated. Appendicular lean mass (ALM) will also be calculated and used to classify those patients with sarcopenia.

Statistical Analysis:

Statistical analysis will be carried out using Statistica version 12 and Stata version 12/IC 12.0. All data will be presented as mean ± SD, and a p value ≤0.05 is considered significant. Student's unpaired t-tests will be used to compare HAQ, BMD, physical activity, patient characteristics, and RA disease activity data between the WBV group and CON group at baseline. To assess the effect of the intervention on primary and secondary outcomes, individual linear mixed models will be used for each dependent variable using relevant covariates where necessary. Random intercepts will be used to account for within person correlation of repeated measures. To test a priori hypothesis, the estimated mean scores at each time point (baseline, post-intervention and

6-months) will be contrasted with baseline values. Additionally, the rate of change in dependent variables across each period (baseline and 3 and 3- 6 month maintenance periods) will be compared to each other. Model fit will be assessed using residual plots and diagnostics.

Discussion:

The present study will contribute to the current field of rheumatology by potentially providing a non-pharmacological means to improve functional ability and attenuate the loss of BMD associated with RA. This study may provide a safe, sustainable exercise intervention for these patients that could potentially improve certain aspects of disease activity, as well as HRQoL and habitual physical activity.

The advantages of the present study over previous exercise interventions in RA include, firstly, the use of a novel therapy in RA. WBV therapy has not previously been used in patients with RA (to the best of our knowledge), and could provide a safe and easy form of exercise for patients who are often unable to participate in strenuous activities. Furthermore, the application of an intermittent WBV programme could potentially exhibit the added benefit (over the previous HRQoL and strength benefits seen following WBV therapy in other rheumatic diseases); of attenuating BMD loss in these patients. Very few studies have focussed exercise interventions on improving or attenuating the loss in BMD in this population, despite the very high prevalence of osteoporosis that exists. Usually, interventions designed to increase BMD are dynamic and strenuous, which is not feasible in an RA population. WBV therapy could provide a solution to this problem.

Secondly, the use of an objective measurement of physical activity could further elucidate the benefits of the WBV intervention by providing an accurate, and detailed description of changes that may occur during and following the WBV intervention. Accelerometry allows for the novel examination of changes in patterns of habitual physical activity in this population following the intervention, which will help elucidate which thresholds of physical activity are affected by WBV therapy. Previous

research conducted by the authors has shown (using accelerometry for the first time in this population as a means to compare physical activity levels to healthy control participants) that patients with RA are extremely sedentary, and that patients with higher levels of physical activity fare better on certain disease activity and HRQoL outcomes (10). The potential ability of WBV therapy to increase physical activity levels could therefore attribute to any changes seen in functional ability, BMD, disease activity and HRQoL in the present study.

Lastly, the inclusion of a post intervention assessment allows the sustainability of the present protocol to be examined. If any changes are observed in any of the primary or secondary outcomes of the present study, it is important to be able to report on whether these changes will be sustained after cessation of the intervention, thereby adding strength to the feasibility of the intervention.

Author contribution:

AP was involved in conceptualisation of the study and wrote the protocol. MT was involved in conceptualisation of the project. JAM was involved in conceptualisation of the project and editing of the protocol.

Funding:

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Competing interests:

The authors have no competing interests to declare.

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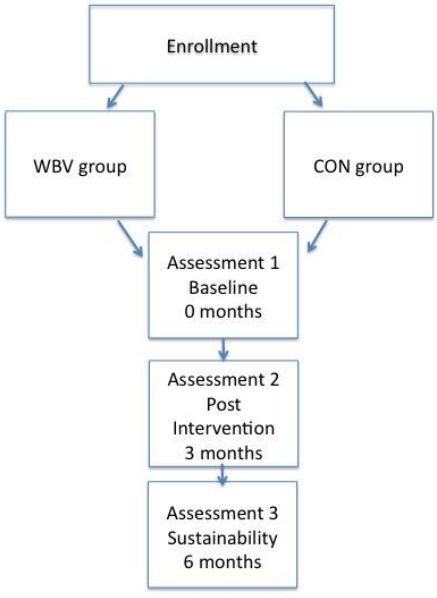
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Figure Legends:

Figure 1. Flow diagram of study design



Appendix 14 – Author Contributions and Acquiescence

Study 1 – The Clinical Utility of Accelerometry in Patients with Rheumatoid Arthritis

	Prioreschi	Hodkinson	Avidon	Tikly	McVeigh
Conceived and designed the research	✓	✓	✓	✓	✓
Acquired the data	✓	✓			
Performed statistical analysis	✓				
Analysed and interpreted the data	✓			✓	✓
Drafted the manuscript	✓			✓	✓

I hereby certify that all co-authors have provided their consent for the inclusion of the paper in the thesis and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.

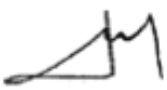
Candidate (Alessandra Prioreschi):



Supervisor (Joanne McVeigh):



Supervisor (Mohammed Tikly):



Study 2 – Changes in Physical Activity Measured by Acceleromtery Following initiation of DMARD therapy in rheumatoid arthritis

	Prioreschi	Hodkinson	Tikly	McVeigh
Conceived and designed the research	✓	✓	✓	✓
Acquired the data	✓	✓		
Performed statistical analysis	✓			
Analysed and interpreted the data	✓		✓	✓
Drafted the manuscript	✓		✓	✓

I hereby certify that all co-authors have provided their consent for the inclusion of the paper in the thesis and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.

Candidate (Alessandra Prioreschi):



Supervisor (Joanne McVeigh):



Supervisor (Mohammed Tikly):

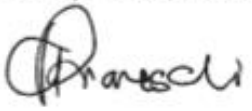


Study 3 – Higher Habitual Activity Levels Are Protective of Bone Mass in Patients with Rheumatoid Arthritis

	Prioreschi	Makda	Tikly	McVeigh
Conceived and designed the research	✓		✓	✓
Acquired the data	✓	✓		
Performed statistical analysis	✓			
Analysed and interpreted the data	✓		✓	✓
Drafted the manuscript	✓		✓	✓

I hereby certify that all co-authors have provided their consent for the inclusion of the paper in the thesis and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.

Candidate (Alessandra Prioreschi):



Supervisor (Joanne McVeigh):



Supervisor (Mohammed Tikly):



Study 3 - Positive effects of a 12 week WBV intervention on functional ability, bone mineral density and fatigue are sustained in a population with established RA

	Prioreschi	Makda	Tikly	McVeigh
Conceived and designed the research	✓		✓	✓
Acquired the data	✓	✓		
Performed statistical analysis	✓			
Analysed and interpreted the data	✓		✓	✓
Drafted the manuscript	✓		✓	✓

I hereby certify that all co-authors have provided their consent for the inclusion of the paper in the thesis and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.

Candidate (Alessandra Prioreschi):



Supervisor (Joanne McVeigh):



Supervisor (Mohammed Tikly):



Protocol - A three month controlled intervention of intermittent whole body vibration designed to improve functional ability and attenuate bone loss in patients with rheumatoid arthritis

	Prioreschi	Tikly	McVeigh
Conceived and designed the research	✓	✓	✓
Drafted the manuscript	✓	✓	✓

I hereby certify that all co-authors have provided their consent for the inclusion of the paper in the thesis and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.

Candidate (Alessandra Prioreschi):



Supervisor (Joanne McVeigh):



Supervisor (Mohammed Tikly):

