ASSOCIATIONS BETWEEN DISEASE ACTIVITY, BIOMARKERS OF BONE TURNOVER AND HABITUAL PHYSICAL ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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DECLARATION

I, Nonhlanhla Hlengiwe Mthembu, declare that this dissertation is my own work with all assistance acknowledged. It is being submitted for the degree of Master of Science in Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

…….. [Signature of candidate]

…….30 August 2018

ABSTRACT

Rheumatoid arthritis, the most common chronic inflammatory auto-immune joint disease, is a leading cause of chronic morbidity. People with rheumatoid arthritis often find activities of daily living difficult to perform due to pain. Together with low levels of physical activity, patients with rheumatoid arthritis have high levels of sedentary behaviour, the combination of which may contribute to poor bone health. Furthermore the chronic use of glucocorticoids, although effective for improving functional capacity, may also result in poor bone health. An active lifestyle however maintains functional capacity and can improve bone health in patients with rheumatoid arthritis. In spite of the benefits of an active lifestyle, patients who suffer from rheumatoid arthritis remain relatively inactive. Detailed and objectively measured physical activity patterns have not been well described in patients with rheumatoid arthritis in a longitudinal study. The value of such detailed information could contribute to informing targeted activity interventions in an effort to additionally improve the functional capacity in rheumatoid arthritis patients following standard treatment of their disease. There is also a paucity of literature that has examined the relationship between physical activity, sedentary behaviour and bone health in people with rheumatoid arthritis. This study aimed to determine: 1) changes in activity behaviours (defined here as physical activity and sedentary behaviour) and bone health following treatment and 2) whether there was a relationship between bone health (using biomarkers of bone turnover) and objectively measured patterns of physical activity and sedentary behaviour (using accelerometry) in newly diagnosed rheumatoid arthritis patients who are starting standard treatment therapy.

Patients with rheumatoid arthritis were referred to a rheumatology clinic and upon diagnosis were invited to participate in the present study. Treatment-naïve patients (n=62) with rheumatoid arthritis who met inclusion criteria participated in this study. Routine therapy (methotrexate) was administered and titrated to target disease remission at 28 weeks after the onset of therapy. Assessments of self-report and clinician-reported patient function as well as activity behaviours were done before and 28 weeks after initiation of therapy. The health assessment questionnaire and the short-form 36-item health survey questionnaire were filled in by the patients with the guidance of a staff nurse. Habitual physical activity and sedentary behaviour were measured using an accelerometer. Biomarkers of bone turnover were assessed from a blood and urine sample. Patients showed a significant ($p<0.0001$) improvement in physical function measured using the questionnaires. The mean short-form

36-item health survey questionnaire score increased from 43.71 to 58.75 and the mean health assessment questionnaire scores decreased from 1.4 to 0.7 after 28 weeks of drug therapy, indicating that the disease-modifying anti-rheumatic drug treatment was successful in improving functional capacity. The accelerometry data showed no significant changes in physical activity and sedentary behaviour after 28 weeks of drug therapy. The participants spent the majority of their time in light intensity physical activity with durations of less than five minute bouts at a time and sedentary behaviour was mostly accumulated in bouts lasting 10-19 min at a time. There was no statistical significance in the change in objective measurements between participants who responded well, moderately and poorly to treatment according to disease assessment score. However, participants who had a good response to treatment increased their number of steps per day by almost 800, while those who had a moderate or poor response to treatment decreased their number of steps by approximately 1000 steps. There was a significant reduction in bone loss (mean Δ N-telopeptides of type I collagen =297.9-173.5 nmol) 28 weeks after treatment therapy.

Overall objectively measured physical activity did not change significantly following disease-modifying anti-rheumatic drug therapy in patients with rheumatoid arthritis. The functional capacity improvement reported using the short-form 36-item health survey questionnaire and the health assessment questionnaire was therefore not indicative of an improvement in activity behaviours as measured by accelerometers. The N-telopeptides of type I collagen and osteocalcin results suggest that disease-modifying anti-rheumatic drug therapy may help to protect the bone of rheumatoid arthritis patients from bone resorption however there is no relationship with levels of physical activity. The ability of only rheumatoid arthritis patients with a good response to treatment to increase their step count perhaps justifies the need to promote changes in lower intensity activity behaviours specifically. In those patients who do not respond well to treatment and who seemingly have difficulty in modifying their activity behaviours, focus on the lower intensity activities and sedentary behaviour may also be a more feasible target of behaviour modification. The results of this study together with future studies will be important in contributing to the development of activity behaviour guidelines aimed at improving the health of those with chronic inflammatory auto-immune joint disease.

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95% confidence interval	95% CI
American College of rheumatology criteria	ACR
Anti-Citrullinated Peptide Antibody	ACPA
Bodily pain	BP
Bone mineral density	BMD
Chris Hani Baragwaneth Academic Hospital	CHBAH
Clinical disease activity index	CDAI
C-reactive protein	CRP
Disease-modifying anti-rheumatic drug	DMARD
Enzyme-linked immunosorbent assay	ELISA
Erythrocyte Sedimentation Rate	ESR
Gamma-carboxglutamic acid	Gla
General health	GH
Habitual physical activity	HPa
Health assessment questionnaire	HAQ
Health assessment questionnaire disability index	HAQ-DI
Low disease activity	LDA
Mental component summary	MCS
Mental health	MH
Metabolic equivalents	METS
Metacarpophalangeal	MCP
Moderate and vigorous physical activity	MVPA
N-telopeptides of type I collagen	NTx
Nuclear factor kappa B	NF-KB

Optic density	OD
Osteocalcin	OC
Outpatient department	OPD
Patient global assessment	PGA
Physical activity	PA
Physical component summary	PCS
Physical functioning	PF
Physician global assessment	PhGA
Principal investigator	PI
Proximal interphalangeal	PIP
Rheumatoid arthritis	RA
Rheumatoid Factor	RF
Role emotional	RE
Role physical	RP
Sedentary behaviour	SB
Short-form 36-item health survey questionnaire	SF-36
Social functioning	SF
Standard deviation	SD
Statistical Analysis system	SAS
Swollen joint count	SJC
Tender joint count	TJC
Treat to target	T2T
United Nations	UN
Vitality	VT
World Health Organization	WHO

Chapter 1: Introduction

1.1 Overview

Rheumatoid arthritis (RA) is an auto immune disease which is associated with hyper-inflammation of synovial joints, especially those of the hands and feet (Boutry et al., 2003). Inflammation at the joints results in cartilage and bone erosion (Goldring, 2003). Cartilage between joints serves as protection padding, preventing bone to bone friction during joint movement. Therefore, joint-cartilage prevents damage of joints as well as pain during movement. The inflammation at the joints as well as degradation of articular cartilage is what causes RA patients to present with symptoms such as joint pain on movement and morning stiffness (Yazici et al., 2004). Furthermore, it is common in RA for the joints on either sides of the eroding cartilage to eventually fuse resulting in joint disability. Predictably, RA also presents with a reduction in joint functional capacity (Welsing et al., 2001). The pain, stiffness and joint disabilities make it difficult for RA patients to perform even normal day to day activities (Kvien, 2004). As a result, RA patients have poor physical activity (PA) and sedentary behavior (SB) levels (Paul et al., 2014).

There is irrefutable evidence to suggest that the healthy population has difficulty in reaching healthy levels of PA (Troiano et al., 2008, Tucker et al., 2011), it is therefore, not surprising that people with diseases that affect mobility and functional performance, such as RA, have an even more difficult time achieving sufficient activity levels (Eurenius and Stenstrom, 2005, Hootman et al., 2003, Minor et al., 1988, van den Berg et al., 2007). In addition to physical inactivity, SB is higher in patients with RA compared to the general population (Prioreschi et al., 2013, Nolte and Rensburg., 2013). The pain and stiffness associated with RA results in the majority of RA patients spending prolonged periods of time lying down or sitting (Iversen et al., 2012). These unfavourable activity behaviours have detrimental effects on overall health but specifically of interest to this study, is bone health (Chastin et al., 2014).

People with RA are already at a high risk of poor bone health (Haugeberg et al., 2002), primarily related to the inflammation in RA that erodes the periarticular cortical bone, which causes excessive amounts of local bone resorption (Schett and Gravallese, 2012). In healthy adults, a high level of SB is associated with low bone mineral density (BMD) irrespective of the amount of PA (Chastin et al., 2014). Therefore, high levels of SB, coupled with insufficient PA, are additional concerns in RA patients as they may deteriorate their bones further.

In addition to inflammation and high SB levels, bone health in RA is negatively affected by drug therapy. Bone mineral density (BMD) in RA patients is reduced by the corticosteroids commonly prescribed by rheumatologists as part of the disease-modifying-antirheumatic drug (DMARD) therapy (Cooper et al., 1995). A study performed on a RA diagnosed population showed that corticosteroids increase the risk of bone fractures (van Everdingen et al., 2002). A combination of low levels of PA, high levels of SB and the drug treatment contributes towards poor bone mass observed in people with RA (Haugeberg et al., 2002, Lee et al., 2008).

The aim of drug treatment in RA is to reduce inflammation at the joints. Reducing joint inflammation reduces pain, stiffness and halts further bone destruction. There is, however, limited evidence to support the notion that anti-rheumatic drugs, by reducing joint pain and stiffness, can increase PA levels and decrease SB in RA patients and whether this can in turn improve bone health. With newer technology (better ways of measuring activity i.e. accelerometers) more detailed descriptions of activity are possible i.e. ways of measuring patterns of PA and SB. Furthermore, an analysis of bio-markers of bone turnover in RA patients' immediately after diagnosis and again after a prolonged period of taking DMARD therapy will contribute towards establishing whether there is a relationship between habitual PA and bone health in this population.

1.2 Problem statement

Most people do not meet the 60 minutes a day of recommended PA guidelines. It may therefore be unrealistic to expect people with RA to reach PA levels comparable with the healthy population. However, there are few studies that objectively detail the patterns of habitual activity and sedentary behaviours of patients with RA. These detailed observations may provide clinicians with the possibility of setting realistic activity behaviour targets for patients being treated with DMARD therapy.

A common co-morbidity associated with RA is low BMD which places patients at risk of osteoporosis and fractures. Both the disease itself and the poor levels of PA and SB can influence BMD in patients with RA. However few studies have looked at the relationship of both factors in conjunction with one another in patients with RA.

1.3 Aims and objectives

This study aims to determine whether self-reported functional capacity and quantity as well as the patterns of habitual activity behaviours, change following DMARD therapy and whether there is a relationship between activity behaviours and bone health in patients newly diagnosed with RA.

This study attempts to answer two main research questions:

1) What are the patterns of, objectively measured, habitual PA and SB in patients with RA and do these patterns change after initiation of DMARD therapy?

2) What is the relationship between PA, SB and bone health in patients with RA?

Therefore the objectives of this study are:

1) To use an accelerometer (ActiGraph GT3X+) to measure and then describe PA and SB patterns in newly diagnosed patients with RA.

2) To determine whether patterns of PA and SB in patients with RA change after 28 weeks of DMARD therapy in relation to subjective measures of physical function.

3) To determine whether markers of bone turnover change after 28 weeks of DMARD therapy.

Chapter 2: Literature review

2.1 Rheumatoid arthritis

2.1.1 History and Epidemiology of rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic chronic autoimmune inflammatory disorder that has a predilection for peripheral synovial joints. It was first identified as a unique form of arthritis by Londré Beauvais in the early 1800s (Storey, 2001). However, it was not until 1854 that Sir Alfred Baring Garrod, looking at the features of RA, formulated the term rheumatoid arthritis (Keitel, 2009, Storey, 2001).

Rheumatoid arthritis affects an estimated 1% of the world's population (Conway and Carey, 2017, Kahlenberg and Fox, 2011). There are only a few studies that have investigated the prevalence of RA in South Africa. One study carried out in 964 participants in Johannesburg showed that South Africa has an RA prevalence of 0.9% (Solomon et al., 1975). The disease is three to five times more common in females (Emery, 2011, Kvien, 2004, McIntosh, 1996) and its prevalence increases with age (Kvien, 2004).

2.1.2 Risk factors and Aetio-pathophysiology of rheumatoid arthritis

Rheumatoid arthritis is a multifactorial disease with both environmental and genetic risk factors playing a role. Some of the known environmental risk factors are blood transfusions, obesity, infectious agents and smoking (Alamanos and Drosos, 2005, Symmons et al., 1997). Furthermore, there are currently 31 confirmed RA risk loci known to date (Stahl et al., 2010). The human leukocyte antigens (HLAs) at 30%, account for the majority of the heritable risk factors of RA (Kurreeman et al., 2007).

The aetiology of RA is not well understood. However, the current concept is that environmental factors in a genetically susceptible individual trigger an immune response which ultimately results in chronic inflammation of the synovial joints (Morovic-Vergles, 2003, Cafaro et al., 2016, Venables, 1989). Chronic joint inflammation causes cartilage and bone erosions (Figure 1) (Mateen et al., 2016). Continued joint erosion and destruction, over time leads to irrevocable joint deformities and reduced mobility of the affected joints (Allaire et al., 2009).

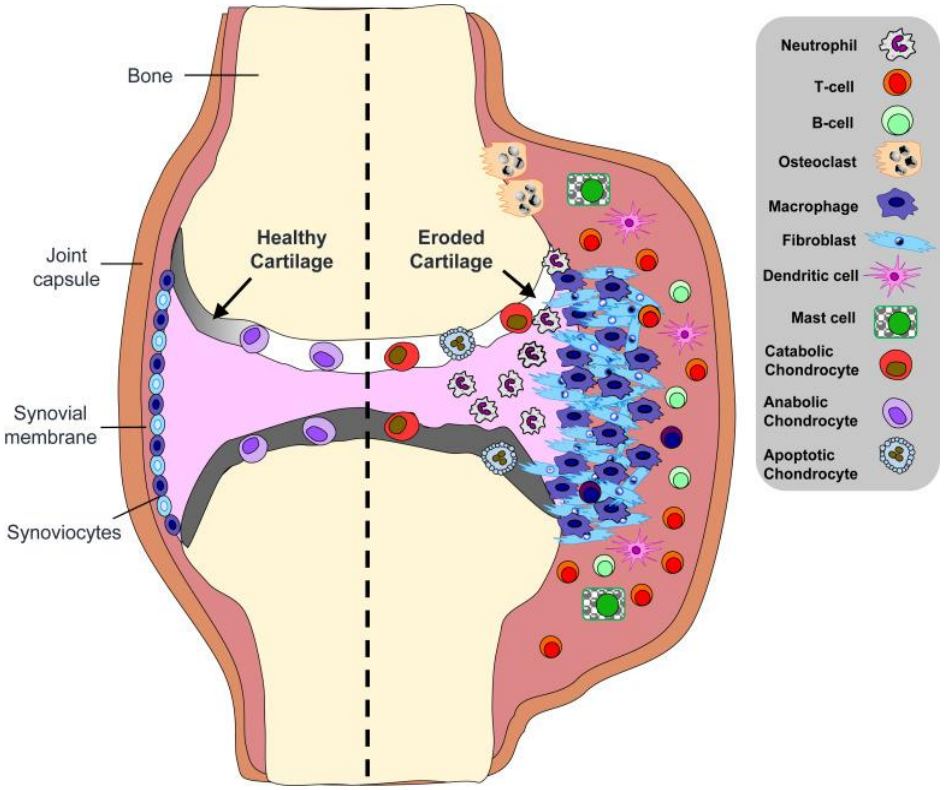

Figure 1 Diagrammatic representation of a healthy synovial joint (on the left) versus an affected synovial joint of a patient with rheumatoid arthritis (on the right).
The diagram shows how inflammatory factors erode cartilage as well as the bone at the synovial joints of rheumatoid arthritis patients. Taken from (Pettit et al., 2001)

2.2 Clinical features of rheumatoid arthritis

Rheumatoid arthritis most commonly presents as swelling, and pain of the wrist and small joints of the hands, with associated early morning stiffness (van der Heijde et al., 1990). The most commonly affected joints are the metacarpophalangeal and proximal phalangeal joints, wrists, elbows, knees and the metatarsophalangeal joints (Grassi et al., 1998). Patients who have at least one unexplainable swelling of a synovial joint are eligible for being evaluated for RA. The clinical diagnosis is usually guided by applying the 2010 American college of rheumatology (ACR) classification criteria for RA as shown in Table 1 bellow (Aletaha et al., 2010).

Table 1 The 2010 ACR classification criteria for RA

Categories:	**Scores**
Joint involvement:	
1 large joint	0
2-10 large joints	1
1-3 small joints	2
4-10 small joints	3
10 joints with at least 1 small joint	5
Blood test of at least one of the following:	
Negative ACPA and RF	0
Low positive ACPA and RF	2
High positive ACPA and RF	3
Reactants of acute phase of at least one of the following tests:	
Normal ESR and CRP.	0
Abnormal ESR and CRP	1
Duration of symptoms:	
Less than 6 weeks.	0
Greater than or equal to 6 weeks	1

The above table is used to evaluate whether or not a person has rheumatoid arthritis (RA). People are eligible to be tested for RA if at least one of their synovial joints is swollen and the synovial swelling cannot be explainable by another disease or injury. They are then scored for each of the four categories shown on the table (joint swelling, blood test, reactants of acute phase of ESR or CRP and symptom duration). Participants who obtain a score of greater than or equal to 6/10 are diagnosed with RA (Aletaha et al., 2010).*ACPA- Anti-Citrullinated Peptide Antibody, RF- Rheumatoid Factor, ESR- Erythrocyte Sedimentation Rate, CRP-, C-reactive protein .

2.3 Natural history and prognosis of rheumatoid arthritis

The natural history of RA is progressive joint destruction and deformities leading to severe physical disability and premature death, if left untreated. Due to the nature of the disease people who suffer from RA are prone to a reduction in functional capacity. Early interventions with disease modifying anti-rheumatic drugs (DMARDs) have been shown to suppress inflammation and thus reduce deformities and physical disability (Aletaha et al., 2010). By so doing, DMARDs are able to improve functional capacity in RA patients.

2.4 Functional capacity in rheumatoid arthritis

People who suffer from RA are prone to impaired functional capacity (Welsing et al., 2001). Evidence suggests that disease activity, which is a measure of inflammatory processes in RA, is the main factor that influences functional capacity in RA patients (Drossaers-Bakker et al., 1999, Naredo et al., 2007, Welsing et al., 2001). Inflammation and stiffness at the joints causes a reduction in joint range of motion (ROM) which in turn reduces functional capacity (Laroche et al., 2006). This is especially true in the metatarsophalangeal (MTP) joints which are involved in walking (Laroche et al., 2006).

An impaired functional capacity can negatively impact daily living in RA patients. Low functional capacity contributes towards promoting high mortality rate in RA patients (Jacoby et al., 1973, Pincus et al., 1984, Uddin et al., 1970, Wolfe et al., 2003). Furthermore, low functional capacity is one of the causes of unemployment, loss of income, reduced social status and increase in dependence in people with RA (Laroche et al., 2006, de Croon et al., 2004). Therefore, it is important to develop effective strategies to improve functional capacity in RA and by so doing, improve their quality of life.

2.5 Management of rheumatoid arthritis

Rheumatoid arthritis is managed both pharmacologically and non-pharmacologically. Since the presentation of RA is unique between individuals, management of RA also varies between individuals, depending on patient response to treatment.

2.5.1 Pharmacological and nonpharmacological management of rheumatoid arthritis

The most effective and commonly used method to improve functional capacity in RA patients, by reducing disease activity, is via drug therapy (Gaffo et al., 2006). The treatment protocol for RA involves the use of disease modifying antirheumatic drugs (DMARDs) as well as prednisone which is a corticosteroid. Both corticosteroids and DMARDs have immunosuppressant properties of varying mechanisms (van Halm et al., 2006).

Methotrexate (MTX) is the most extensively used DMARD. The role of MTX is to reduce joint inflammation in RA patients. Methotrexate in the treatment of RA is only given in low doses. A low dose of MTX (15mg-25mg/week) has three main mechanisms of action: To increase anti-inflammatory cytokines, reduce pro-inflammatory cytokines and increase adenosine (Œwierkot et al., 2006). Leflunomide is a DMARD given at 20mg/week for the treatment of RA and functions to inhibit pyrimidine synthesis. Even patients who are intolerant or non-responsive to MTX are responsive to Leflunomine (Silverman et al., 2005). Prednisone which is often prescribed in combination with DMARD is a glucocorticoid and therefore it can limit progression of joint damage caused by inflammation. Prednisone is especially effective in drug naïve patients with early active RA (van Everdingen et al., 2002).

Drug therapy in RA is aimed at limiting joint destruction and retard bone and cartilage erosion and thus induces disease remission (Mottonen et al., 2002). The presumption is that with reduced pain, RA sufferers can have an improved quality of life and functional ability (Smolen et al., 2010).

In addition to drug therapy, there are a number of nonpharmacological interventions to manage RA. These interventions include physical activity (PA) modification, occupational therapy, dietary modification, surgery and mobility aids such as canes, walking-frames and wheelchairs (Vliet Vlieland and van den Ende, 2011). Nonpharmacological therapy is important in adjunct to pharmacological therapy. This is because drug therapy does not stop the degenerative process observed in RA (Forestier et al., 2009). Therefore, it is important to develop additional strategies to manage RA.

2.6 Management of outcomes in rheumatoid arthritis

In order to evaluate the effectiveness of treatment therapies, RA patients return to their rheumatoid clinic for follow-up assessments. During the follow-up sessions, the

rheumatologists measure the change in the patient's functional capacity as well as bone health.

2.7 Subjective measurement of treatment success

The most affordable and convenient method of measuring functional capacity in RA patients is via the use of questionnaires (Welsing et al., 2001). A number of questionnaires have been developed to monitor functional capacity in different illnesses. The two widely used questionnaires in RA are the Short Form 36-item health survey questionnaire (SF-36) and the Health Assessment Questionnaire (HAQ). HAQ is the most commonly used questionnaire to measure functional capacity in RA (Bruce and Fries, 2005, Fries et al., 1980). The SF-36 questionnaire is a valid measure of functional capacity in RA (Jenkinson et al., 1993, McCarthy et al., 2007).

2.7.1 Short form 36

A survey was carried out to evaluate the legitimacy, dependability, and appropriateness of the SF-36 questionnaire in North East Scotland (Garratt et al., 1993). The survey involved 1700 patients with lower back pain, suspected peptic ulcer, or varicose veins as well as 900 healthy consenting volunteers. The SF-36 was reported to be tolerable to patients, an acceptable measure of health status and internally consistent (Garratt et al., 1993). The validity of the SF-36 questionnaire has been shown in a number of other studies (Garratt et al., 1993, Jenkinson et al., 1993, McCarthy et al., 2007). In one particular study SF-36 was shown to be a valid tool for the assessment of adult health status when tested on RA patients (Kosinski et al., 1999). There are a number of other studies that used the SF-36 to evaluate the change in physical functionality in RA patients after drug therapy and have shown good validity and reliability (Genovese et al., 2008, Tugwell et al., 2000).

South Africa has 11 official languages most of which are spoken in Gauteng (Prinsloo et al., 2005). Attempts to translate the SF-36 have been made to accommodate South Africans who do not speak English (O'Keefe and Wood, 1996). However, most healthcare facilities in South Africa use the English translation of the SF-36 questionnaires which are then verbally translated by a nurse for those who don't understand English. A study was performed on Xhosa speaking HIV positive patients in South Africa to evaluate the reliability of SF-36 after it was translated into Xhosa (O'Keefe and Wood, 1996). The O'Keefe and Wood, (1996) study showed that the SF-36 questionnaire is reliable and valid when translated into one of the

South African languages (Xhosa). However, because there is as yet no study to validate the SF-36 when translated into the 9 other South African languages, and for the sake of practicality, in this study the English version of the form was used.

2.7.2 Health assessment questionnaire

The Health Assessment Questionnaire (HAQ), published in 1980, is the most widely used questionnaire that was developed specifically to quantify the long term influence of multiple chronic illnesses on affected individuals (Bruce and Fries, 2003). There are a number of studies that have used the HAQ to evaluate disability change in RA patients following drug therapy (Breedveld et al., 2006, Elliott et al., 1993, Genovese et al., 2008, Prioreschi et al., 2014b, Quinn et al., 2005, Tugwell et al., 2000). The HAQ has been shown to be effective in assessing fine movements and therefore, it is ideal for the evaluation of functional capacity in RA due to the nature of the disease (Bruce and Fries, 2005).

There is no literature that shows that the HAQ has been translated into any South African language in addition to English. Therefore, as it is with SF-36, in the South African population HAQ requires verbal translation for patients who do not understand English.

2.7.3 Functional capacity and activity behaviours

It is evident that questionnaires such as the SF-36 and HAQ are effective in assessing improvement in functional capacity in RA patients during treatment. However, functional capacity is also influenced by physical behaviours. Low physical Activity (LPA) levels cause a reduction in muscle tone and ROM (Plasqui, 2008). A reduction of muscle tone and ROM aggravates the functional impairment in RA patients. Therefore, improving muscle strength and endurance as well as ROM by improving physical activity (PA) is important to maintain functional capacity (Plasqui, 2008). A recent study showed that the more physically active an individual is the easier it is for them to perform everyday activities more effortlessly (King et al., 2018). Improved PA also reduces risks of falls in older people and it therefore maintains independence (King et al., 2018).Thus, improving PA levels in RA is beneficial to the patients' quality of life. For this reason, WHO in their International Classification of Functioning, Disability and Health proposed that research focus more on the habitual activity levels of daily living of people with musculoskeletal conditions rather than their disability levels (Verbunt et al., 2009). However, before PA can be assessed in RA, the different activity behaviours that can be measured in RA should be well understood.

2.8 Physical activity and sedentary behaviour

Physical activity (PA) occurs when energy is expended by any movement of the body produced by skeletal muscles (Figure 2) (Caspersen et al., 1985). Physical activity includes habitual physical activity, sports, and any activity performed during leisure time (Dishman et al., 2001). A PA guideline was developed by World Health Organisation (WHO) in order to improve and maintain health in the adult population. This guideline can be seen in Table 2. In brief, muscle strength activities are recommended on at least two days of the week. Furthermore, it is recommended that an adult participate in at least 150 minutes of moderate PA, 75 minutes of vigorous activity or a combination of the two per week in order to maintain health (Elsawy and Higgins, 2010). There appears to be no literature of a PA guideline recommended specifically for people with mobility disorders such as RA.

Table 2 Physical activity guidelines for adults

- Muscle strength activities on at least two days and 150 minutes of moderate aerobic activity per week.
- Muscle strength activities on at least two days and 75 minutes of vigorous activity per week.
- Muscle strength activities on at least two days and a mix between 150 minutes of moderate activity and 75 minutes of vigorous activity per week.
- To achieve additional health benefits one can double the three points above.
- Aerobic exercise should last at least 10 minutes.
- Muscle strengthening activities should involve all major muscle groups and should be carried out until difficulty to do a repetition is reached.

Adapted from: World Health Organization 2010 (Elsawy and Higgins, 2010).

Table 2 shows the physical activity guidelines for adults as recommended by the World Health Organization. These guidelines were confirmed in the latest Physical Activity Guidelines Adversary Committee Science Report (PAGACSR) released at the beginning of 2018. However, the PAGACSR pointed out that the previous guideline recommending that aerobic exercises should be at least 10 minutes long may not be accurate. It is incongruent with recommendations such as taking the stairs instead of the elevator or parking further away from your place of work, as these activities usually take less than 10 minutes to carry out. Assuming aerobic exercises to only be beneficial if they are at least 10 minutes in duration is

an assumption that activities such as ‘taking the stairs’ to be useless. The 2018 PAGACSR therefore highlights the importance of monitoring all types of activities even in patients with mobility disorders e.g. RA, as there may ultimately be benefits to performing any intensity and duration of activity. Studies measuring and describing detailed activity behaviours in patients with RA are therefore needed.

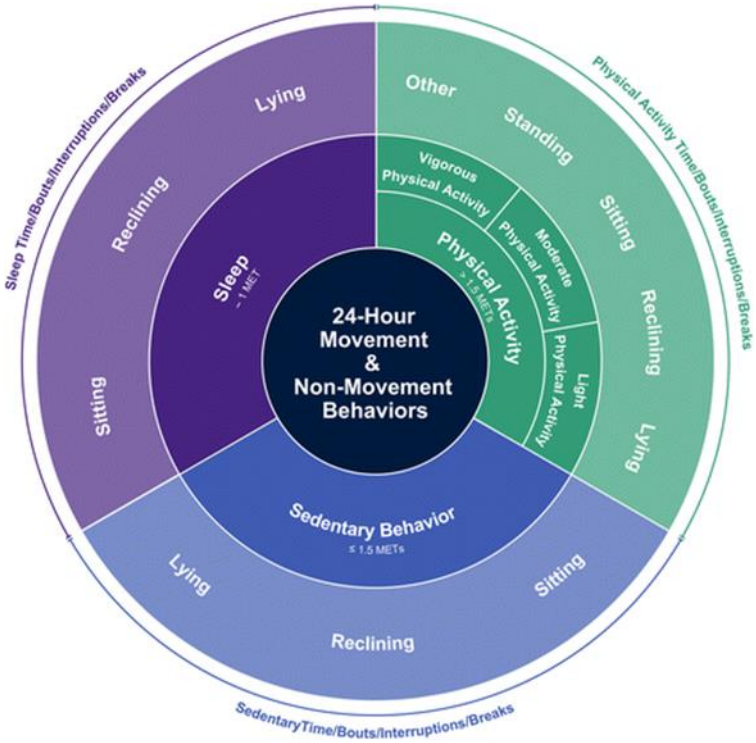

Figure 2: The movement and non-movement behaviour that illustrates the definition of sedentary behaviour, physical activity and sleep.Taken from: Sedentary behavior research network (SBRN)–terminology consensus project process and outcome (Tremblay et al., 2017).

The Sedentary Behaviour Research Network (SBRN) suggested a consensus for the definition of SB in the year 2012, and this idea was agreed on by 52 researchers internationally (Tremblay et al., 2017). It was agreed that SB can be defined as any behavior during wake time performed with an energy expenditure of ≤1.5 metabolic equivalents (METS), in a reclining, sitting, or lying posture (Kim et al., 2015, Tremblay et al., 2017). This definition is now the most widely cited and agreed on (Arundell et al., 2016) (Figure 2). Sedentary behaviour is part of the activity spectrum that has not been well studied in patients with RA (Fenton and Kitas, 2016).

2.9 Physical activity in rheumatoid arthritis and healthy people

The average healthy population in low-middle income countries is 17-91% less active than is recommended by global PA guidelines for health (Oldridge, 2008; King et al., 2018) (Table 2). Further evidence of the lack of the general population's ability to take part in PA can be seen in a study performed on a Canadian healthy adult population, over a period of two years. The study showed that only 15% of adults reach PA levels recommended by the PA guidelines (Colley et al., 2011). Another study showed that only one quarter of women and one third of men meet international PA guidelines in a healthy population in UK (Miles et al., 2007).

An active lifestyle can be associated with psychological benefits such as stress reduction, high quality of life as well as a positive outlook on life (Berger et al., 1996). Furthermore PA helps maintain normal functional capacity; it conserves muscle strength and endurance as well as range of motion (Plasqui, 2008). Therefore, living an active lifestyle can be beneficial to people who have musculoskeletal conditions such as RA patients (Brodin et al., 2008, Harkcom et al., 1985). Indeed, the benefits of living an active lifestyle have been shown in people living with RA (Eurenius and Stenstrom, 2005). However, the functional limitation in people with RA causes them to be relatively physically inactive.

A study was carried out in 21 countries (using self-report questionnaires) over a period of three years. The study showed around 80% of RA participants, in the majority of the 21 countries evaluated did not meet the PA levels recommended for by PA guidelines (Larkin and Kennedy, 2014). Eurenius and Stenstrom, (2005) also found significantly lower levels in self-reported habitual PA in persons who suffer from RA compared to age matched healthy individuals. Another study was carried out using self-report questionnaires in 252 Dutch citizens with RA. This study showed that patients who suffer from RA are less physically active in a week compared to people not diagnosed with RA (van den Berg et al., 2007).

2.10 Sedentary behaviour in rheumatoid arthritis and healthy people

Independent of PA levels, excessive SB is negatively associated with health outcomes (de Rezende et al., 2014, O'Donoghue et al., 2016, Harrington et al., 2011, Owen et al., 2010a, Owen et al., 2010b). The majority of today's healthy population spends a generous amount of time in SB (Grontved and Hu, 2011). Sedentary behaviour is associated with being

overweight, cancer, type 2 diabetes mellitus, metabolic syndrome, cardiovascular conditions and premature death (Dunstan et al., 2010). Furthermore, prolonged SB has been named as an important mortality cause determinant (de Rezende et al., 2014, Dunstan et al., 2012, Manns et al., 2015).

In addition to low levels of PA people with RA are highly sedentary. Rheumatoid arthritis patients have been observed to spend over seven to eight hours of wake time in a day sedentary (Gilbert et al., 2016, Paul et al., 2014, Prioreschi et al., 2013, Prioreschi et al., 2014a). Some studies have recorded RA patients spending even more time sedentary compared to the healthy population (Prioreschi et al., 2013, Nolte and Rensburg., 2013) Patients with RA are already at a significantly higher risk of suffering from chronic illnesses when compared to the healthy population. Therefore prolonged SB in this population puts them at an even higher risk of developing chronic illnesses (Thomsen et al., 2015). Moreover, inactivity in RA patients puts them at risk of developing clinical depression and cardiac illnesses (Fenton et al., 2017, Katz and Yelin, 1995). Some of the proposed reasons behind the sedentary lifestyle in RA are pain, lack of motivation and fear of self-harm (Wilcox et al., 2006).

As previously mentioned, people with RA suffer from a reduced ROM, joint stiffness and pain on movement. Due to these symptoms RA patients are less active and more sedentary than the healthy population. Given that the healthy population also has a hard time reaching healthy levels of PA, it is perhaps more practical for RA patients to attempt to reduce SB rather than increase PA (Thomsen et al., 2015). More recent evidence suggests that people with RA should break up their sedentary time more frequently for benefits to health, one benefit being to bone health (Prioreschi et al., 2015). Furthermore, taking active breaks between sedentary periods may enhance or improve cardiovascular health as well as improve bone mineral density (BMD) in RA patients (Prioreschi et al., 2015, Carter and Gladwell, 2017). This evidence suggests that it is not only the total volume of SB and PA that puts people with RA at risk of poor health, but also the pattern of accumulation of time spent in SB. This could mean that a guideline that can help the RA patients intentionally breakup the times they spend sedentary may be beneficial to them. In order to be able to manipulate the activity patterns of people with RA, one has to be able to accurately and objectively quantify the levels of PA and SB patterns in RA.

2.11 Methods of measuring physical behaviour in rheumatoid arthritis

Studies that have investigated the PA and SB levels of RA have mostly used subjective methods of assessment (van den Berg et al., 2007, Konijn et al., 2016). There is a paucity of longitudinal studies that have used objective methods to measure sedentary behaviour in addition to PA in RA patients.

2.12 Measurement of physical activity and sedentary behaviour

A few studies have used self-report methods to evaluate changes in PA levels following treatment in RA patients. In these studies people diagnosed with RA have been shown to have low PA level compared to the healthy population regardless of DMARD therapy. One of such studies was performed by van den Berg et al., (2007) in Netherlands to evaluate PA levels in 400 female RA patients and compare them to a healthy control. The study of van den Berg et al., (2007) showed that participants between the ages of 45 and 65 had lower PA levels in a week compared to age matched controls, despite being on DMARD therapy. Physical activity levels in the van den Berg et al., (2007) study used the Short QUestionnaire to ASsess Health-Enhancing PA (SQUASHEPA) to assess PA levels. Another study was carried out by Konijn et al., (2016) to evaluate change in PA after treatment using the SQUASHEPA. The study showed that the RA patients who did not clinically respond to DMARD therapy were less active after treatment compared to RA patients who responded to DMARD therapy (Konijn et al., 2016). The lower levels of PA have been confirmed by Prioreschi et al., (2014a) who used accelerometers to objectively monitor PA in people diagnosed with RA and compared them to healthy controls in a low-middle income country.

There are not many longitudinal studies that objectively observed the changes in activity behaviours in RA patients following DMARD therapy in low-middle income countries. Objective measures of RA patient's response to DMARD could be useful in evaluating whether a change in functional capacity after DMARD therapy reflects the change in activity behaviours. The activity patterns of PA and SB in RA patients can be measured objectively with the use of accelerometers.

2.13 Objective measurement of physical activity and sedentary behaviour

The objective measurement of PA and SB eliminates bias that may be introduced through the use of self-reporting methods (Haskell, 2012). Therefore the use of accelerometers is recommended in studies that assess activity behaviours as they are not influenced by subjective opinions of the study participants (Verbunt et al., 2009).

2.13.1 ActiGraph

A systematic review of 42 articles showed that objective measures of activity have an advantage over self-report due to the lack of bias (Verbunt et al., 2009). One of the most commonly used objective devices to measure activity behaviours is the ActiGraph accelerometer. ActiGraphs have been used in a number of studies to measure PA and SB (Ridgers et al., 2012) and one such monitor- the GT3X is widely used in PA research (Sasaki et al., 2011). The GT3X+ is a tri-axial accelerometer (McMinn et al., 2013), monitoring acceleration in three planes: the vertical (VT), anterio-posterior (AP) and medio-lateral plane (Sasaki et al., 2011). The GT3X+ can be worn on the wrist or the waist to monitor PA levels, however; it is most useful for ambulatory movement when worn around the waist (Rowlands and Stiles, 2012). The validity of the ActiGraph when waist-worn was confirmed in a study where participants were asked to perform different activities of varying intensities whiles wearing three GT3X+ accelerometers on the left and right wrist as well as the waist (Rowlands and Stiles, 2012). The GT3X+ has also been found to be highly accurate in monitoring sedentary time when tested on 36 healthy participants who were asked to perform light and sedentary activities under controlled settings (Carr and Mahar, 2012). The findings in the study of Carr and Mahar (2012) imply that GT3X+ is a reliable measure for PA and SB. The GT3X+ has also been used to measure PA and SB in RA patients (Yu et al., 2015, Fenton et al., 2017) The ability for the GT3X+ to accurately measure SB makes GT3X+ a good choice for the current study since RA patients spend prolonged periods of time in SB (Paul et al., 2014, Gilbert et al., 2016, Prioreschi et al., 2013).

2.14 Physical activity and sedentary behaviour in rheumatoid arthritis following treatment

Due to the lack of RA specific PA guidelines, advice given to patients are not consistent among treating physicians. As mentioned above remaining physically active and limiting the time spent sedentary has health benefits for patients with RA. However, the objective

improvements (if any) in PA and SB have not been extensively studies in RA patients following treatment. If functional capacity has been seen to subjectively improve, it should follow then that habitual daily activities should improve and SB should decrease following treatment. However, it appears that there is a scarcity of studies that have evaluated detailed assessments of activity behaviours using accelerometers in a low-middle income country (Prioreschi et al., 2014a, Prioreschi et al., 2015). Furthermore, studies of this nature are limited in a South African population. In order to develop guidelines for the RA patients, detailed data describing the activity behaviours of people with RA is required. Importantly, both the quantity and the patterns of accumulation of time spent in PA and SB influence health in RA. The data should include daily patterns of activity such as when maximal PA is accumulated, bouts of activity and the intensity of such activities. The above mentioned data have not been described using objective methods in a sample of patients with RA. There is a paucity of longitudinal studies that analyse the change in patterns of PA and SB in RA patients living in low-middle income countries (Table 3). Table 3 gives a brief summary of PA and SB investigations performed on RA patients with the aid of accelerometers. The patients in these studies were already on DMARD at the start of the research and the date of diagnoses was not considered. Furthermore, the participants who participated in the longitudinal studies on Table 3 were followed up after no more than three months. The importance of these differences is that it is difficult to conclude that the change in PA during follow-up investigations is not due to the differences in the duration that the patients have been on treatment. It is also possible that the three months was not enough time to see lifestyle changes in these participants. Finally, the cross-sectional studies on Table 3 may be subject to more contributing factor to the results than longitudinal studies. Prioreschi et al., (2014b) did use accelerometers to investigate change in PA and SB levels after the initiation of DMARD therapy in participants recruited from low-middle income countries. However, they did not go into detail explaining the accumulation of PA and SB in this population, furthermore, they had a sample size of 21 and participants had only been on treatment for a short period of time (three months) (Prioreschi et al., 2014a). Similarly Prioreschi et al., (2015) looked at PA and SB level differences after a short period of time (two weeks) in their 18 RA participants recruited from a low-middle income country.

Since the patterns of SB also contribute towards determining health risks in RA patients it is important to investigate the patterns of SB in this population. Analysis of these patterns i.e. breaks in sedentary time, duration of breaks between sedentary periods, as well as the intensity of the breaks in sedentary time, will provide a more detailed assessment of SB in RA

patients. The study of SB as an independent activity behaviour in RA patients has also not been detailed. Because RA patients could improve their functional capacity by minimizing the time spent being sedentary then it should follow that following treatment these patients should decrease their SB after treatment but this has not yet been investigated in South Africa.

Table 3 Summary of studies that measured PA and SB change in rheumatoid arthritis patients after treatment

Author	Country	Type of study	RA participants	Disease duration	Device used	Outcome measures /findings
(Henderson et al., 1995)	USA	Longitudinal	n=23, with control (n=23), ages 5-11 years, Sex not stated.	Corticosteroid naïve JRA patients, disease duration = 4.2 (2.5).years	Caltrac accelerometer, worn on a belt around the waist, centered over the right hip.	PA was lower in JRA patients than in controls (P = 0.05), daily body movement was similar. JRA had less participation in organized sports (P = 0.01).
(Lee et al., 2012)	Chicago USA	cross-sectional (over 1week)	n=176, age = 23–86 years, females=83%	13.5 ± 10.2 years	GT1M ActiGraph accelerometer, worn on a belt around the waist at the natural waistline (right hip) in line with the right axilla.	42% RA were inactive (i.e: did not meet physical activity guidelines). Inactivity strongly related to lack of strong motivation (65%)
(Prioreschi et al., 2013)	South Africa	Cross-sectional (over 2 weeks)	n=50, with control (n=22), age=48(13), female=100%	Pre-diagnosed RA of varying durations (no stated).	Actical accelerometers. For 2 weeks (on hip of dominating leg). HAQ-DI and SF-36.	The participants with RA were more sedentary than control by 11% (p=0.002), HAQ-DI negatively correlated to PA in test group (p=0.03). More physically active RA patients scored better on SF-36.
(Prioreschi et al., 2014a)	South Africa	Longitudinal (3 month follow-up)	n=18 with control (n=18) age=50(14), female=100%	Pre-diagnosed RA of varying durations (not stated).	Actical accelerometers. For two weeks during baseline and follow-up (on hip of dominating leg).	There was a significant drop in SB (p=0.01), a significant increase in light activity (p=0.04), and no changes in MVPA after three months of DMARD therapy.

(Prioreschi et al., 2015)	South Africa	Longitudinal (1 week follow-up)	n=29, age=54, female=100%	Established RA, NBM= 9.6 (8.5) years and LBM =16.5 (10.6) years.	Actical accelerometers. For one week during follow-up only (on hip of dominating leg).	Patients with normal bone mass had 2 hr less sedentary activity ($p<0.01$), and 70 min more light activity ($p<0.01$), >50 min more moderate activity ($p<0.01$) in a day compared to low bone mass patients. Normal bone mass RA patients broke up SB more frequently ($p=0.03$).

RSA: Republic of South Africa, RA: Rheumatoid arthritis, LBM: Low bone mineral density, USA: United States of America, CHBH: Chris Hani Baragwaneth Hospital, NBM: Normal bone mineral density, PA: Physical activity, HAQ: Health assessment questionnaire, MVPA: Moderate or vigorous physical activity, SB: Sedentary Behaviour, JRA : Juvenile Rheumatoid arthritis, GT1M: First ActiGraph model. HAQ-DI: Health assessment questionnaire disease index, DI: Disease index

2.15 Bone health in rheumatoid arthritis

RA patients are at a greater risk of a number of comorbidities compared to their healthy counterparts (Avina-Zubieta et al., 2008; Cobb et al., 1953). However, one of these co-morbidities that will be studied in the current study is that of poor bone health. Therefore a secondary outcome of this study is the effect of treatment of RA on bone metabolism. Wegierska et al., (2016) indeed reported that people with RA more commonly develop osteoporosis when compared to the healthy population. Patients with RA are prone to poor bone health due to a number of factors. Osteoporosis is one of the most common bone comorbidities. According to WHO, osteoporosis is defined as a bone mineral density loss of approximately 2.5 SD or more below that of a healthy adult (a T-score of <-2.5 SD). An inactive lifestyle, SB, glucocorticoids, hyper-inflammation and poor diet is some of the risk factor for developing osteoporosis. People who suffer from musculoskeletal conditions usually have most of the risk factors of developing osteoporosis and they are thus more prone to developing osteoporosis (Wegierska et al., 2016).

During intense immunologic and inflammatory processes, inflammatory cells such as activated macrophages lymphocytes, and plasma cells, infiltrate the synovial lining, resulting in the destruction of bone integrity (Goldring, 2003). The unique tendency of bone resorption seen in RA is due to the production of a variety of factors potent to osteoclast (bone resorbing cells) activation and differentiation, such as receptor factors of ligand NF-KB, at the synovium (Goldring, 2003, Pettit et al., 2001). Evidence shows that RA patients have low bone mineral density (BMD) and a 2-fold increase in the risk of osteoporosis (Haugeberg et al., 2000).

Bone health can also be negatively affected by the glucocorticoids used to treat pain and inflammation in RA. Glucocorticoids are detrimental to bone health (Wegierska et al., 2016, van Staa et al., 2003). Whereas DMARD has no negative effects on bone health in RA patients (Minaur et al., 2002, Tascioglu et al., 2003), glucocorticoids, commonly taken with DMARD, are known to cause osteoporosis (Carpinteri et al., 2010). A longitudinal study carried out over three years on 133 RA patients revealed a reduction in BMD in RA patients on prednisone (Buckley et al., 1997). Continuous remodeling of bone is a crucial process of maintaining the functional integrity and structure of the skeleton (Leeming et al., 2006). The two cells responsible for this process are osteoblast and osteocytes. Osteoblasts are cells required for bone formation. Osteocytes are mature osteoblast cells imbedded in the bone

matrix to form new bone. Chronic use of corticosteroids reduces the viability of osteoblasts and osteocytes resulting in osteoporosis (Haugeberg et al., 2002). Corticosteroids are thus detrimental in a population that is already at high risk of developing osteoporosis due to hyper-inflammation of the joints, low bone mineral density (BMD) and low PA levels (Kim et al., 2010).

2.16 Biomarkers of bone turnover

Studies show that there are biomarkers in the serum as well as urine that are indicative of the status of bone turnover (Leeming et al., 2006, Berry et al., 2011). These biomarkers play a big role in predicting risk of bone fractures (Leeming et al., 2006). The two commonly used biomarkers are serum osteocalcin (OC) and urinary cross-linked N-telopeptides of Type I collagen (NTx) (Berry et al., 2011, Lian and Gundberg, 1988, Szulc et al., 1996). Although other biomarkers of bone turnover do exist, for the purpose of the current study OC and NTx was used as OC and NTx have been shown to be reliable indicators of bone formation and bone loss respectively (Karlsson et al., 1995, von Schewelov et al., 2006). A number of studies have used OC and NTx to evaluate bone turnover in RA (Seriolo et al., 2002, Hall et al., 1995, Al-Awadhi et al., 1999, Iwamoto et al., 2003).

2.16.1 Osteocalcin

Osteocalcin (OC) is a specific gene of osteoblasts (Wei and Karsenty, 2015). As mentioned above, osteoblasts are cells responsible for the formation of new bone. Therefore, OC is excreted into the blood stream during bone formation. Osteocalcin breaks up to form the amino-acide gamma-carboxyglutamic acid (Gla) which can be excreted in the urine (Lian and Gundberg, 1988). The amount of OC measured in blood serum is a good indicator of bone formation (Karlsson et al., 1995).

2.16.2 Urinary cross-linked N-telopeptides of Type I collagen

Research has suggested that the dominant process that results in bone loss in RA patients is osteoclastic activation (Iwamoto et al., 2003). Therefore, in order to understand the pathogenesis of bone loss in RA it is best to examine bone resorption markers in addition to bone formation markers (Iwamoto et al., 2003). Urinary cross-linked N-telopeptides of Type I collagen (NTx) has a high specificity to bone resorption (Xue et al., 1999, von Schewelov et

al., 2006). During bone resorption NTx is released into the urine and is a good measure of bone loss (von Schewelov et al., 2006).

2.17 The effect of physical activity and sedentary behaviour on bone health

In adults a bone replacement cycle called bone remodeling occurs every 100-1000 days, depending on bone health i.e. the more repairs the bone needs, as is the case in RA, the shorter the time between remodeling (Eriksen et al., 2010). Old bone is removed by osteoclasts and replaced by new bone by osteoblasts. Assuming that the adult does not change the amount of weight the bones have to carry, old bone is replaced by the same amount of new bone (Parfitt, 1994). The reason why bone is replaced is because it starts to get too old to perform haemopoiesis and homeostasis (Parfitt, 1994). Thereafter, bone health is influenced by individuals lifestyle choices as well as illnesses e.g. RA.

In addition to the inflammatory processes that occur in RA, low PA levels may also have an influence in bone development. Low levels of PA further increase the negative effect on bone in a population already at a high risk of poor bone health (Braun et al., 2015). There is evidence to suggest that whether or not an individual was active during growth determines how strong their bones are later on in life (Warden et al., 2007). During growth, exercise promotes new bone to be laid on the periosteal surfaces. In so doing, bone can be kept strong till adulthood (Warden et al., 2007). However carrying out a physically active lifestyle in the middle aged and elderly population is also beneficial to bone health. Studies have found a strong association between inactivity and non-fatal fractures in elderly people (Braun et al., 2015, Stevens et al., 2006). Another study performed on retired athletes showed that reduction in PA decreases bone mineral density (BMD) (Nordstrom et al., 2005). A systematic review study was carried out to investigate the benefits of exercise in adults (Guadalupe-Grau et al., 2009). The latter study revealed that there are certain forms of PAs that increase and maintain bone growth in adults. High-impact activities like jumping as well as weight lifting stimulate bone growth in adults (Guadalupe-Grau et al., 2009). On the other hand, most studies report that the main benefit of high-impact exercise and weight lifting in postmenopausal women is merely maintenance of bone mass (Guadalupe-Grau et al., 2009). A number of studies have evaluated and confirmed the benefit of strengthening and aerobic exercise in RA patients (Ekblom et al., 1975, Harkcom et al., 1985, Nordemar et al., 1981). A study performed on

newly diagnosed RA patients in Soweto (South Africa), suggested that high levels of habitual activity are protective of bone (Prioreschi et al., 2015).

The benefits of exercise effects to bone health in a physically inactive and highly sedentary population could also play a role in improving the bone health of patients with RA. Indeed a study that was conducted in RA patients that exposed them to a whole body vibration intervention for three months showed that bone health improved in a similar cohort of patients (Prioreschi et al., 2014b). However, it appears that most studies evaluate the benefits of structured exercise in RA. The relationship between habitual PA and especially SB in relation to bone health in RA patients has not been well explored. RA patients often report an improvement in functionality post treatment (Prioreschi et al., 2014b, Maini et al., 2004). It is possible that an improved functional capacity may result in improved habitual PA levels. It is worth investigating whether the change in functional capacity and habitual PA has any effect on bone health in RA patients.

2.18 Problem Statement

Accurately and objectively assessing the physical functionality of RA patients before and after treatment may assist in better understanding the effect DMARD therapy has on improving quality of life. It is also important to monitor the effect DMARD therapy has on bone health because one of the co-morbidities that occur in patients with RA is poor bone health. A number of studies have used self-report methods to study functional capacity in patients with RA. However, it is not clear whether an improved functional capacity is equivalent to an improved habitual PA level and reduction in sedentary time and thus an improvement in dependence and quality of life.

Functional capacity is influenced by PA. People who live active lives have better muscle tone and ROM. Furthermore older people who live active lives fall less and therefore are less likely to sustain fractures. Both these benefits of an active lifestyle lead to the possibility of the improvement in the independence of people with RA and therefore their quality of life. There are few studies that have investigated the changes in objective activity behaviours (PA and SB levels) after RA patients have been on DMARD therapy in low-middle income countries. There are studies that have used self-report methods to measure PA and SB in RA patients following treatment. These methods of research, although effective, can only evaluate the quantity changes in activity behaviours and not the patterns of accumulation of PA and

SB. The use of accelerometers, such as ActiGraph, to study activity behaviours in people with RA can give us a more detailed picture of how mobility and functionality may be affected in the daily lives of RA patients.

There is a shortage of longitudinal studies that subjectively investigates PA as well as SB levels in adult newly diagnosed with RA. PA and SB patterns have not been described longitudinally in adult population diagnosed with RA in low-middle income countries such as South Africa. The importance of this type of analysis is that whereas total time spent sedentary has shown to be similar between healthy and diseased populations (Balkau et al., 2008), the pattern of accumulation of sedentary time may be different and might suggest other reasons for the prevalence of an inactive or sedentary lifestyle (Chastin et al., 2010). Moreover, the study can contribute towards developing interventions or guidelines that can improve the functional capacity of those who suffer from RA. Furthermore, analyzing the change in biomarkers of bone turnover with change in PA patterns may assist in evaluating whether PA patterns influences bone health as poor bone health is a common co-morbidity in patients with RA. An improvement in activity behaviours can potentially improve functional capacity, bone health and the overall quality of life of people living with RA.

Chapter 3: Materials and Methods

3.1 Study design

This study was a longitudinal study where subjective measures of patient functional capacity and health status, objectively measured habitual physical activity (PA) and sedentary behaviour (SB) (using an accelerometers) and biomarkers of bone turnover (from a blood and urine sample), were made at baseline and following 28 weeks of disease modifying antirheumatic drug (DMARD) therapy in newly diagnosed patients with RA. The study was approved by the Human Research Ethics Committee (M170296) of the University of the Witwatersrand (Appendix A).

3.2 Participants

Patients (n=80) attending the rheumatoid outpatient clinic for the first time at the Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, Johannesburg, volunteered to participate in this study. The participants had been referred to the rheumatology clinic by their general practitioners and were assessed by the rheumatologists at the RA clinic, to determine eligibility for the current study. These patients were diagnosed, with RA according to the 2010 American College of Rheumatology (ACR) criteria. The 2010 ACR criteria comprises of seven classifications as listed in table 1 (Cader et al., 2011, Aletaha et al., 2010).

Men and women between the ages of 18 and 55 years who were diagnosed with RA and had not yet started DMARD treatment were then eligible to participate in the study. Participants were excluded if they had any co-morbidity that affects physical activity or if they suffered from any other physical deformities that limited mobility e.g. osteoarthritis. In addition, patients who used assistive walking devices for any mobility problems except for RA were excluded. Participants were also excluded if they had congestive heart failure, a history of stroke or any neurological problems, chronic obstructive pulmonary disease (COPD) or gout as determined from a general health questionnaire. At the baseline visit, 71 eligible participants had all procedures explained to them before being asked to sign an informed consent form.

Of the 80 RA patients invited for this study, at baseline four patients were under the age of 18 and five were wheelchair bound. For the follow up visit, four were considered defaulters (missed more than four weeks of DMARD therapy), one developed cancer, another one

dropped out of the study and three had late follow-up dates and so could not complete the study. Therefore 62 RA patients participated in the study from baseline to follow up (Figure 3).

3.3 Outline of procedures

At the first visit to the clinic (baseline), after reading about the study from an information sheet and having the study verbally explained to eligible participants, they were asked to sign a consent form (Appendix B). After consultation with a rheumatologist, a validated Health Assessment Questionnaire (HAQ), disease activity score (DAS) questionnaire as well as the SF-36 were filled out in order to assess physical disability due to RA. A venous blood and urine sample was also taken at baseline for the analysis of biochemical markers of bone turnover. An accelerometer was then given to the participants to wear for seven days for the assessment of habitual physical activity and sedentary behaviour levels. Following 28 weeks of treatment, participants visited the outpatient department (OPD) for a follow up assessment, where the same procedures were repeated.

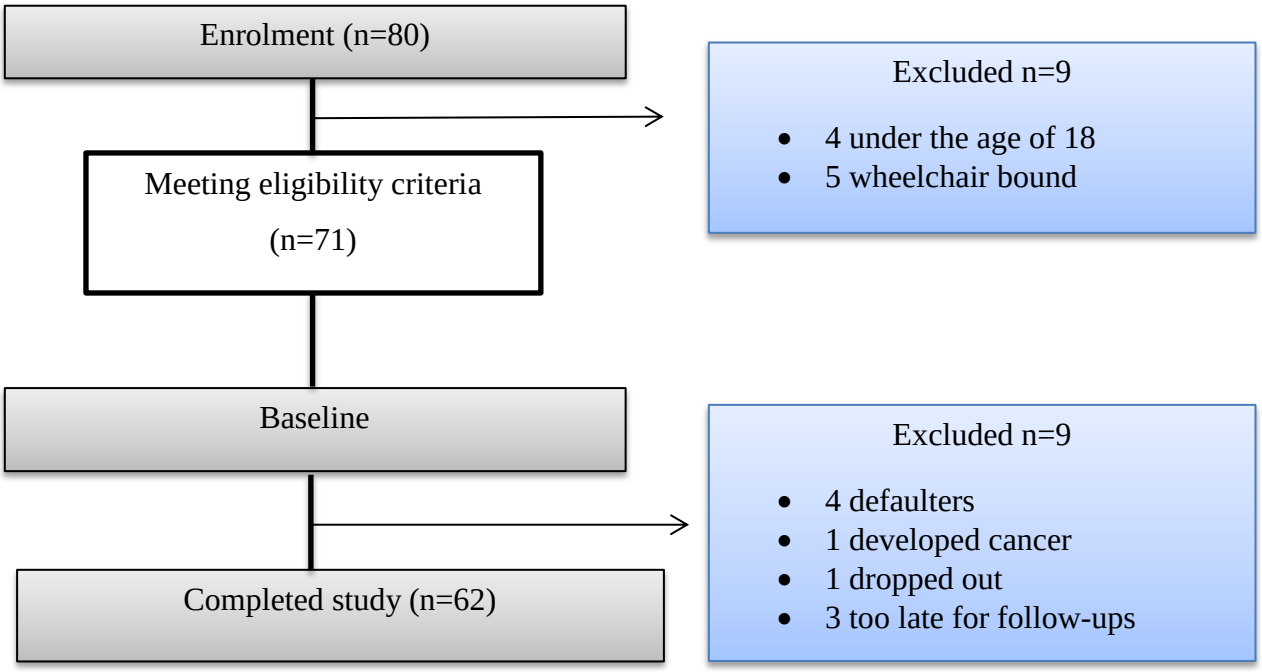

Figure 2 Diagrammatic representation of participant recruitment, and study outline at baseline and after 28 weeks of DMARD therapy.

3.4 Sample size calculation

Based on previous literature that has shown a 17% reduction in average time spent in sedentary activity in patients with RA before and after DMARD/drug therapy, an *a priori* sample size calculation showed that a total sample size of 54 was required in this study to detect significant effect of DMARD therapy on sedentary activity with a power of 90% (Prioreschi et al., 2014a). An additional 26 participants were recruited to account for an expected dropout rate of approximately 25%. Therefore the total sample size recruited was 80.

3.5 Treat to target drug therapy protocol

A specific Treat to Target (T2T) drug therapy protocol was followed by the attending rheumatologists at CHBAH whereby they adjusted patient DMARDs to reach each individual's disease activity target (determined by the patients disease activity score DAS 28). From initiation of therapy, every four weeks the rheumatologist would adjust the patient's

DMARDs, if necessary, until they achieved the treatment target, which is low disease activity (LDA) or disease remission (Tan et al., 2017).

Figure 4 illustrates the progression of the treatment therapy protocol. At the baseline visit patients were initiated on methotrexate (15mg/week) and prednisone (5-7.5mg/day). Methotrexate was increased by 5mg/week until disease activity target was reached. A maximum dose of 25mg/week was given. Thereafter, if disease target was still not met at the subsequent visit, chloroquine (200mg/day) and sulfasalazine (500mg/twice daily) (twice daily) was added to the methotrexate maximum dose. Lastly, if disease activity target was still not met by the next visit, leflunomide (20mg/day) was initiated. Depending on disease activity, the attending rheumatologists then may have decided to increase or decrease DMARD therapy accordingly. Prednisone was prescribed if the patient had no contraindications, such as peptic ulcers, psychoses or infections, at the rheumatologist's calculated judgment. Initial drug response was anticipated to occur by six months of drug therapy and/or drug modification (National Clinical Guideline for Management and Treatment in Adults, 2009). Therefore, in this study, all patients were followed up after 28 weeks of initiation of drug therapy to increase chances of reaching initial drug response.

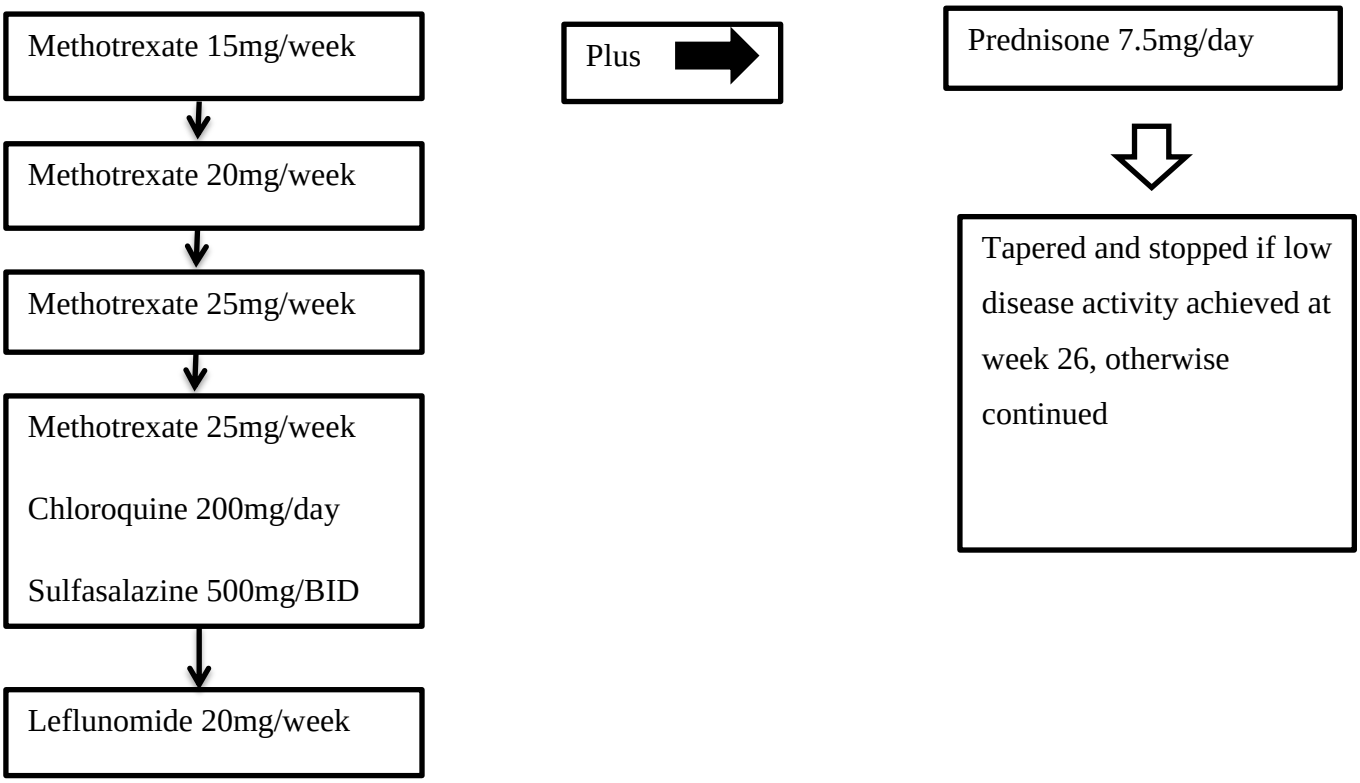

Figure 3 Flow diagram of treatment protocol for rheumatoid patients at CHBH: treatment progression beyond 28 weeks only occurred if RA patients are unresponsive to the first drug.

3.6 Functional capacity questionnaires

The Health Assessment Questionnaire (HAQ) and Short Form 36 (SF-36) were completed at baseline and after 28 weeks of DMARD therapy by patients at the rheumatoid clinic with the assistance of a staff nurse. These questionnaires gave the practitioner an idea of the ease at which the patient was able to perform normal everyday activities, as well as an indication of their psychological state (Guillemin et al., 1991). The subjective measurement of patient functionality was used to assess the progress of patients throughout their treatment.

3.6.1 Health assessment questionnaire

The Health Assessment Questionnaire (HAQ) assesses patient perceived functional ability by providing a score of functionality between 0 and 3, where 0 indicates good functionality and 3 indicates severe functional disability. Over the past 20 years the HAQ has shown to be an

effective, valuable and sensitive self-report measurement technique to evaluate health status (Bruce and Fries, 2003).

The HAQ can be divided into the following components: HAQ- Disability Index (HAQ-DI), HAQ VAS Pain Scale and other dimensions of the full HAQ (such as drug toxicity). For the purpose of this study the HAQ-DI was used, which is the disability assessment component of the HAQ. Patients were asked to complete the HAQ-DI with the guidance of a staff nurse. It assesses the activities of both lower and upper limbs as well as fine movements of the hands. The HAQ-DI includes 20 questions divided into eight categories. Patients are asked if they are able to perform activities involving dressing, rising, eating, walking, hygiene, reaching, gripping and habitual activity (Ramey et al., 1992). There are at least two questions per category (Appendix C). The minimum score that may be obtained is 0 indicating very good physical function. The maximum score is 100 the closer the score is to 100 the greater the disability (Bruce and Fries, 2003).

3.6.2 Short form 36-item health survey questionnaire

The short form 36- item health survey questionnaire (SF-36) is a popular subjective method used to evaluate the quality of life in chronic patients attending health care facilities (Appendix D). The two components measured by the SF-36 are mental component summary (MCO) and physical component summary (PCO). Both these components were examined within the following eight scales: bodily pain (BP), general health (GH), mental health (MH), physical functioning (PF), role emotional (RE), role physical (RP), social functioning (SF), as well as vitality (VT) (Lins et al., 2016). The total score can be calculated with the aid of an online SF-36 calculator provided in the following link: http://www.rand36calculator.com/. The maximum score obtainable is 100% (indicating good functionality) and the lowest score obtainable is 0% (indicating poor functionality) (Lins et al., 2016).

3.7 Disease activity score

Disease activity scores (DAS 28) were also calculated using a DAS 28-calculator on excel (Appendix E), using measures that are taken from the 28 joints examined by the rheumatologist. DAS 28 is a clinical index of disease activity in RA is calculated using the patient's tender-joint-count (TJC), swollen-joint-count (SJC) and erythrocyte sedimentation rate (ESR; mm/hr) (Fransen and van Riel, 2005). DAS 28 was calculated for each patient at baseline and again after 28 weeks of treatment. Using the EULAR response criteria, patients

were categorized into three groups depending on their improvement and their present value in DAS 28 scores which gave an indication of their response to treatment (Table 4) (Matsui et al., 2007). For example, good responders to DMARD therapy were those who improved their DAS 28 score by greater than 1.2 and had a present DAS 28 score of at least 3.2. Participants with moderate response to DMARD therapy may have had a DAS 28 score improvement of greater than 1.2 and a present DAS 28 score of at least between 3.3 and 5.1 or a moderate responder may have had a DAS 28 score improvement of between 0.7 and 1.2 and a present DAS 28 score of between 3.2 and 5.1. Participants who did not respond to DMARD therapy may have had a DAS 28 score improvement of less than or equal to 0.6 regardless of their present DAS 28 score measurement.

Table 4 Summary of interpretation of DAS 28 scores according to the EULAR response criteria

	DAS 28 improvement		
Present DAS 28	**> 1.2**	**> 0.6 and ≤ 1.2**	**≤ 0.6**
≤ 3.2	Good response	Moderate Response	No Response
> 3.2 and ≤ 5.1	Moderate response	Moderate Response	No Response
> 5.1	Moderate response	Moderate Response	No Response

3.8 Biomarkers of bone turnover

A 10 ml venous blood and urine sample was taken for the assessment of the bone formation marker, serum osteocalcin (OC) and the bone resorption marker, urinary cross-linked N-telopeptides of Type I collagen (NTx) respectively using commercially available ELISA kits. A qualified nurse drew the blood samples from the brachial vein. The blood was centrifuged and serum aliquoted for storage at -80℃ for later analysis. Urine was frozen two hours after collected, and stored at -80°C. The samples were calculated from the equation generated from the standard curve reported in nanograms/milligrams.

3.8.1 Serum osteocalcin

The assaying of osteocalcin for the current study was performed according to manufacturer's instructions using a commercially available human osteocalcin ELISA (Elabscience®, WuHan, China). Briefly, venous blood was drawn into serum separator tubes from the participants (10ml). The blood was then centrifuged at 1000×g for 20 minutes at room temperature after 2 hours of collection. Plasma was extracted via a pipette from the centrifuged blood and stored in conical eppendorf tubes (1.5ml) at -80°C until analysis. On the day of assaying, all reagents and samples were brought to room temperature (18-25°C) without the use of heat. 100µL of each sample, standards (40, 20, 10, 5, 2.5, 1.25, 0.625 ng/mL) and blank was vortexed and pipetted into the wells of a 96-well microtiter plates in duplicates. The wells were gently mixed, covered with a sealer and incubated for 90 minutes at 37°C. Biotinylated detection antibody was added to each well and they were again covered and incubated for an hour at 37°C. The wells were washed three times with approximately 350µL of previously prepared wash buffer using an automated washer. 100µL of horseradish peroxidase (HRP) conjugate was added to the wells. Thereafter, the well tray was covered and incubated for 30 minutes at 37°C. The wells were washed five times as previously explained. 90µL of substrate solution was added to each well. The wells were covered and incubated for 15 minutes at 37°C. 30µL of stop solution was added to each well. Within five minutes of the stop solution the optic density/absorbance (OD) of each well was read using a micro-plate reader set to 450 nm.

A standard calibration curve was generated from the known standard samples and the unknown concentration of the blood samples were calculated from this curve and reported in nanometres (ng/mL).

3.8.2 Urinary cross-linked N-telopeptides of type I collagen (NTx)

The assay of urinary cross-linked N-telopeptides of type I collagen (NTx) was performed according to the manufacturers guidelines (Osteomark® NTx Alere HealthCare, Kempton Park, South Africa). Urine was collected in a urine cup with a tight fitting lid and stored at -80 °C until assaying. Before the assay the urine and reagents were allowed an hour to thaw and brought to room temperature (18-25°C) without the use of heat. 25µL of each calibrator, control and urine specimen was pipetted into each well of 96-well microtiter plates in duplicate. 200µL of the working strength conjugate solution was pipetted into each well. The wells were covered using a plate sealer and gently swirled on a flat surface for 7 minutes. The plates were incubated at room temperature (18-25°C) for 90 minutes. 1:101 dilution of Chromogen/Buffered solution was prepared 10 minutes before the end of the well incubation. The wells were washed 5 times with the working strength wash solution using an automated plate washer (set to dispense 350µL of wash solution per well). 200µl of the previously prepared Chromogen/Buffered was pipetted into each well and the plate was covered with a sealer. The plate was incubated at room temperature for 15 minutes. 100µL of stop solution was pipetted into each well and the plate was swirled gently on a flat surface for 7 minutes. The plates were allowed to sit at room temperature (18-25°C) for five minutes before the absorbance was read using a micro-well plate reader at 450nm with a reference filter of 630nm.

A standard calibration curve was generated from the known standard samples and the unknown concentration of the blood samples were calculated from this curve and reported in nanometres (nmol).

3.9 Measurement of physical activity and sedentary behaviour

The ActiGraph was used to collect data on habitual physical activity (PA) and sedentary behaviour (SB) at baseline and again after 28 weeks of DMARD therapy. The ActiGraph was worn by participants, around the waist, for 24 hours/day for seven days at baseline and again after 28 weeks of DMARD therapy. The ActiGraph was attached to an elastic nylon strap which the participants wore like a belt around their waist. Participants were asked to remove the ActiGraph only when they showered, bathed or swam. After seven days of accelerometer wear, the accelerometers were collected at the next possible visit to the hospital or the principal investigator (PI) arranged to collect the accelerometer from the patient at a location

most convenient to them. Furthermore, on the seventh day participants were also asked to verbally report to the PI on their average weekday and weekend sleep and wake times over the seven days. The sleep and wake time was recorded and later used to confirm wake wear time from the accelerometry readings. ActiGraph data were downloaded and processed using a custom built SAS program (v 9.3, SAS Institute, Cary, NC, USA). Sleep time and non-wear time was removed from the raw data using a validated algorithm (McVeigh et al., 2016). Where distinct sleep times could not be determined the data were visually inspected in conjunction with self-reported sleep times. Non-wear time was classified as one minute intervals with consecutive zero counts for a minimum of 90 minutes, with an allowance of up to 3 minutes of counts between 0 and 50 (Choi et al., 2011). The remaining data were referred to as the wear period. For a day to be classified as valid, the wear period had to consist of a minimum of 10 hours (600 minutes). Only data from participants with four or more valid days of wear were included in analyses. These data were classified as time spent sedentary, time spent in light activity, time spent in moderate to vigorous activity (MVPA), daily number of breaks in sedentary time and time spent in sedentary breaks. Common cut-points were used to class each minute as sedentary (<100 counts per minute, cpm) (Matthews et al., 2013), light intensity activity (100 and 1951 cpm), moderate-vigorous intensity activity (1952 and 5724 cpm) or vigorous (<5724 cpm) (Freedson et al., 1998). The pattern of accumulation of sedentary, light and moderate to vigorous activity behaviours during an average day was also extracted from the data.

3.10 Data analysis

All data, where appropriate, were reported as mean (SD) unless otherwise stated. Descriptive statistics were used to detail the patterns of habitual physical activity and sedentary behaviour in the RA patients at baseline. An unpaired t-test or a Mann-Whitney U test (non-parametric data) was used to determine differences in descriptive characteristics between the baseline and 28 week follow up time points. A linear mixed effects model was then used to assess whether total volume and patterns of activity behaviours and bone turnover changed following 28 weeks of DMARD treatment. The model was adjusted for age, BMI, and disease activity (measured using the SF-36 score) and in the case of PA and SB as it was reported as absolute time wear-time was also included as a confounder. Non-normally distributed data were analyzed using a generalized linear mixed model and the data were again adjusted for age, BMI, sex, SF-36 score and wear-time (and reported as absolute time). The fixed effect used in

the models was visit (baseline or 28 weeks) and the random effect used was participant. An intercept only model was used. Following treatment patients were stratified according to whether they responded well to treatment using the change in the DAS 28 score between baseline and 28 weeks (good response, moderate response and no response). The change in activity behaviours from baseline to 28 week assessment were then compared between these three groups using a one-way ANOVA, adjusting for age, BMI, sex, baseline SF-36 score and wear-time. The relationship between activity behaviours and bone turnover was also investigated using a multiple linear regression, adjusting for BMI, age, SF-36 score and sex.

A p-value of less than 0.05 was considered significant. Statistical analysis was performed using SPSS version 23 software (SPSS Inc., Chicago, IL, USA).

Chapter 4: Results

4.1 Summary of data analyzed

4.1.1 Participants included in the study

Of the 80 RA patients invited to participate in this longitudinal, 71 enrolled into the study but only 62 completed the study (Figure 3). Of the 71 patients who started the study, nine patients did not meet the study requirements (seven females and two male). Four of the female participants who met the study requirements were removed from the study due to defaulting. At Chris Hani Baragwanath Academic Hospital (CHBAH) a patient is considered a defaulter if they miss more than four weeks of DMARD therapy. One male patient reported that he had developed cancer and had started cancer treatment; therefore he could no longer take part in the study. Another female patient declined to wear the accelerometer during the follow up week. All the patients who did not complete the study had BMIs within the range of BMI of the remaining study group (BMI: 25-27 kg/m^2). The participants were all DMARD naïve and newly diagnosed with rheumatoid arthritis (RA). The participants were between the ages of 18 and 55 years.

4.1.2 Collected data

Two patients had invalid ActiGraph wear-time for baseline and two did not have valid ActiGraph wear-time after 28 weeks of DMARD therapy. Due to unforeseen technical issues, data from nine ActiGraph devices could not be retrieved for baseline and data from ten ActiGraph devices could not be retrieved after 28 weeks of DMARD therapy. The final numbers of activity data available for analysis was 53 for baseline and 52 after 28 weeks of DMARD therapy (Figure 5).

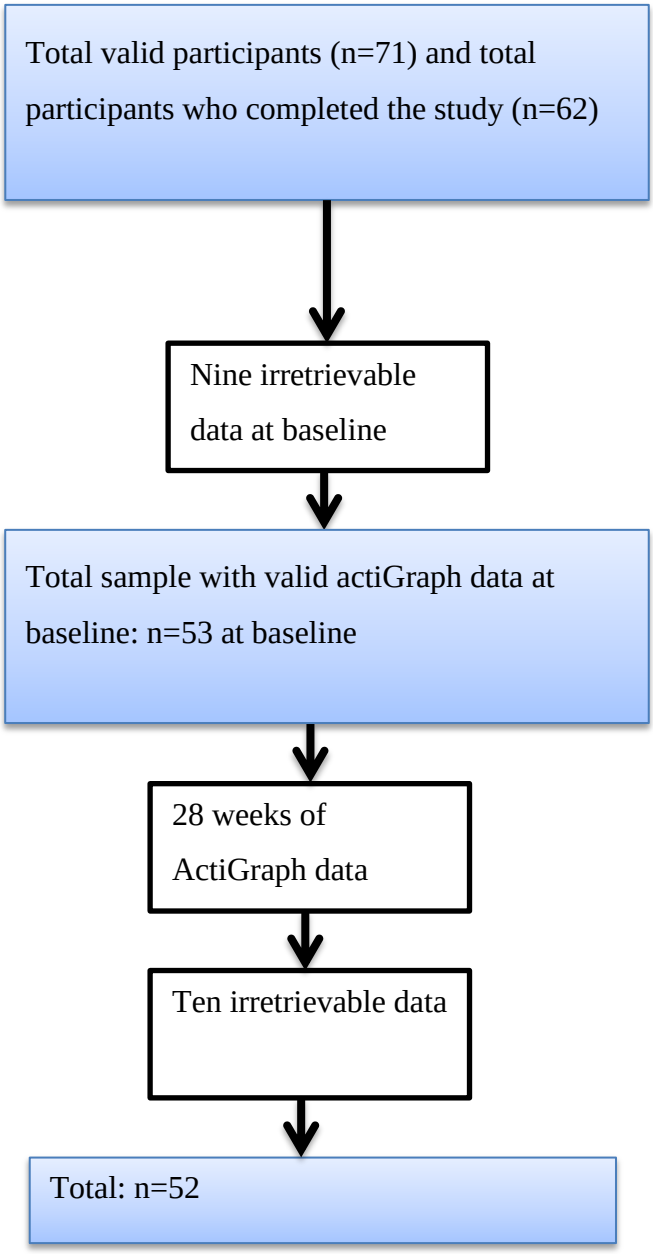

Figure 4 Flow diagram of ActiGraph data obtained from the 62 valid participants at baseline and after 28 weeks of DMARD therapy.

4.2 Overview

4.2.1 Demographics

Table 5 shows the characteristics of the patients who completed the study. The study group contained 74% (n=46) female and 26% (n=16) male participants. The majority were middle-aged people who were overweight (average BMI = 27kg/m^2).

4.2.2 Summary of subjective results

Table 5 also shows that the HAQ score (which indicates the level of disability) was significantly lower in patients after 28 weeks of DMARD therapy when compared to baseline. The scores obtained for overall physical function (recorded by the SF-36) significantly improved after 28 weeks of treatment. These results show that when subjectively assessed, the RA patients significantly improved in physical functioning after 28 weeks of DMARD therapy. Most of the patients (48%) had a good response to the DMARD treatment, 25% had a moderate response and 27% of all patients showed no response to DMARD therapy.

Table 5 Descriptive characteristics of participants at baseline and after 28 weeks of DMARD therapy

	Baseline (n=62)	28 weeks (n=56)	p-value
Age (years)	52.9 (10.1)	52.5 (12.8)	0.9135
BMI (kg/m^2)	27.5 (6.9)	26.9 (6.6)	0.8480
SF36 overall	43.7 (39.3-48.1)	58.8 (54.4-66.4)	<0.0001
Physical functioning	53.6 (42.8-55.9)	65.1 (22.5-38.1)	<0.0040
Role physical	24.6 (15.0-34.2)	47.3 (7.8-21.3)	0.0004
Bodily Pain	36.3 (27.8-40.6)	56.1 (25.2-42.5)	<0.0001
Social Functioning	49.1 (43.9-58.2)	66.5 (31.2-51.0)	<0.0001
Mental Health	61.5 (54.1-63.0)	66.8 (31.3-48.6)	<0.0400
Role Emotional	24.2 (15.9-34.9)	53.9 (10.6-25.1)	<0.0001
Vitality	50.1 (43.9-53.1)	54.9 (23.0-37.3)	<0.0200
General Health	50.5 (44.9-53.4)	59.5 (24.8-40.9)	0.0001
HAQ	1.4 (1.2-1.6)	0.7 (0.5-0.9)	<0.0001
DAS score	4.9 (2.4-8.6)	3.1 (0.2-8.5)	<0.0001
Counts per day	230079 (113446)	252111 (114545)	0.3000

Data are means (95% CI) except for DAS score which is median (min-max) with standard deviation (SD) for the relevant body composition characteristics as well as age, weight, height, BMI and counts which are means (SD). BMI body mass index, SF36 - short form 36-item health survey questionnaire mean, HAQ - Health assessment questionnaire, DAS-Disease activity score.

Figure 6 is a radar graph that visually shows the SF-36 scores in participants during baseline and after 28 weeks of DMARD therapy. There was a significant increase in the overall SF-36 scores from baseline to after 28 weeks of DMARD therapy (p=0.0001; Table 5) indicating an improvement in functionality. Within each analysed domain, the greatest improvement was seen in Role physical and Role emotional (p=0.0004 and p=0.0001 respectively).

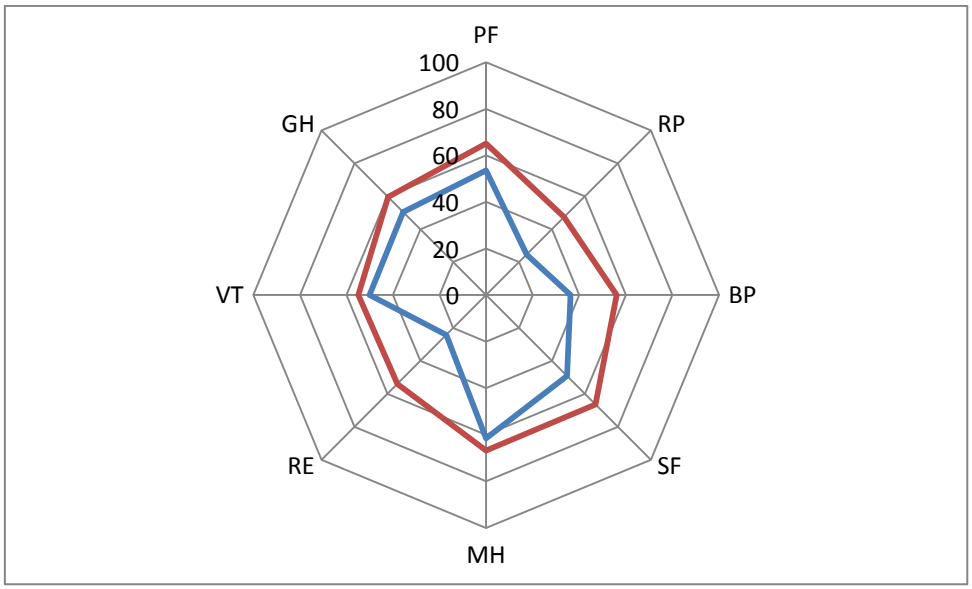

Figure 5 Radar plot showing the SF-36 scores before treatment and 28 weeks after DMARD therapy.

The blue lines represent the SF-36 scores of the participants before DMARD therapy and the red lines represent the SF-36 scores of the participants after 28 weeks of DMARD therapy. PF- Physical functioning ,RP- Role physical, BP- Bodily Pain, SF- Social Functioning, MH- Mental Health, RE- Role Emotional, VT- Vitality, GH- General Health.

4.3 Activity behaviours

Table 6 shows the total volume of time spent in sedentary behaviour, light and moderate physical activity as well as the patterns of these activity behaviours recorded by the ActiGraph accelerometers before and after DMARD therapy. There were no differences in the total amount of time spent in any of these activity behaviours following DMARD therapy compared to before treatment. In addition the patterns of activity (prolonged bouts of sedentary behaviour) were not different following DMARD therapy. The number of steps of the participants improved by 343 (296-390) steps per day, however, this again was not significantly different compared to the baseline number of steps ($p=0.37$).

Table 6 Accelerometer measured total volumes and patterns of activity behaviours of patients before and after treatment.

	Baseline (n=62)	**28 weeks (n=56)**	**p-value**
Awake wear time (min/day)	927.7 (894.7-960.8)	954.4 (921.7-987.2)	0.15
SB (min/day)	556.8 (529.3-584.2)	579.4 (552.2-606.6)	0.13
SB ≥ 20 (min/day)	192.4 (170.3-214.6)	210.1 (188.1-232.0)	0.15
SB ≥ 30 (min/day)	116.6 (98.4-134.7)	128.5 (110.5-146.5)	0.24
SB bout duration (min/bout)	5.8 (5.3-6.2)	5.9 (5.5-6.4)	0.56
Breaks from SB (n/day)	99.4 (93.7-105.1)	100.7 (95.1-106.4)	0.69
SB breaks (min/break)	3.8 (3.5-4.0)	3.7 (3.5-4.0)	0.82
Light PA (min/day)	350.7 (323.2-378.1)	354.9 (327.6-382.1)	0.74
Light PA bout (min/bout)	3.3 (3.1-3.5)	3.3 (3.1-3.5)	0.95
MVPA (min/day)	19.1 (13.5-24.7)	21.6 (16.1-27.2)	0.53
MVPA bouts (n/day)	2.2 (1.8-2.5)	2.3 (2.0-2.7)	0.43
Steps (n/day)	6065 (5290-6839)	6408 (5586-7229)	0.37
Meeting PA guidelines (%)	30.9	38.9	

Data are means (95%CI). SB-sedentary behaviour, Light PA- Light physical activity, MVPA – Moderate to vigorous PA. Data are adjusted for age, BMI, SF-26 score, disease activity and weartime. A bout is defined as consecutive epochs of the same intensity of activity.

Figures 7 and 8 show how sedentary behavior (SB), light physical activity (LPA) and moderate/vigorous physical activity (MVPA) was accumulated during the day as a percentage of awake wear time that was spent in activities of differing bout lengths during the day, before (Figure 7) and after (Figure 8) DMARD therapy. At both time points (before and after DMARD therapy), patients spent a similar proportion of their day accumulating most of their SB in bouts lasting between 10 and 19 minutes (baseline: 14.6% and 28 week: 14.3%). The majority of the participant's LPA was accumulated in short bouts lasting less than 5 minutes (baseline: 16.5% and 28 weeks 16.2%). There were however no significant differences in PA and SB patterns of accumulation between baseline and 28weeks after DMARD therapy ($p > 0.05$).

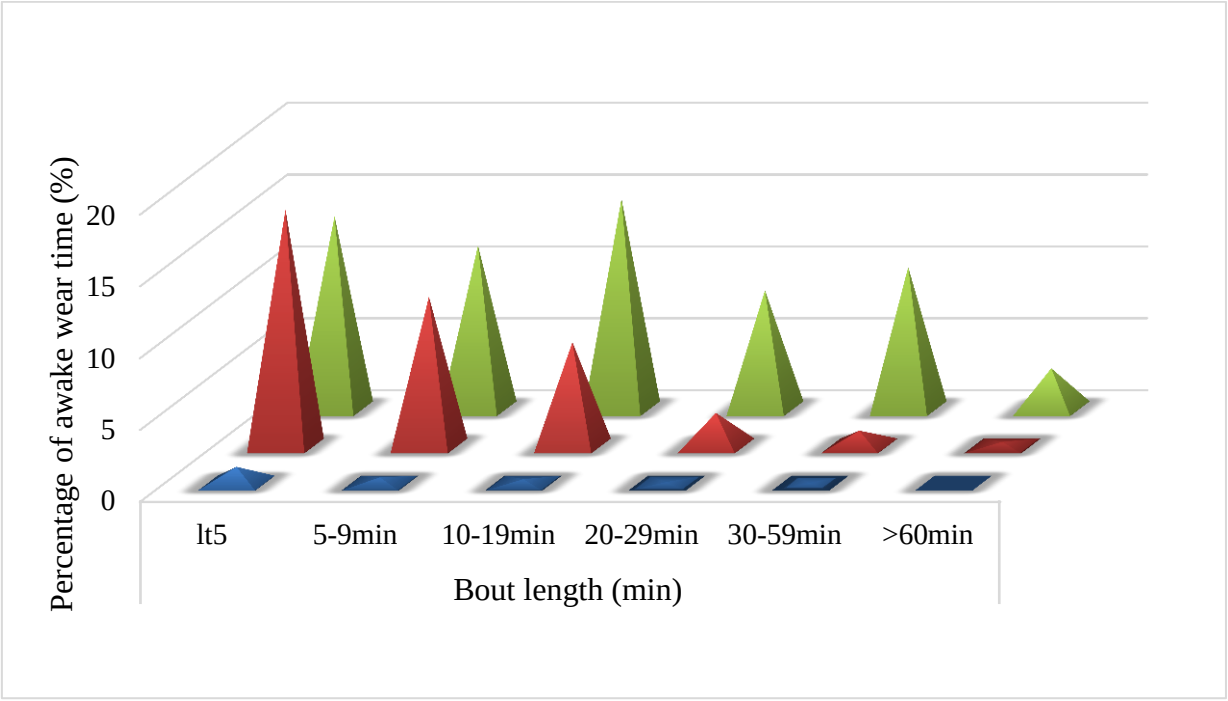

Figure 6 Proportions (%) of the total wake wear time spent in bouts of different lengths (lt = less than) for each of the different intensity activities before DMARD therapy (baseline). Green bars represent sedentary behaviour (SB), red bars represent light physical activity (LPA) and blue bars represent moderate to vigorous intensity activity (MVPA).

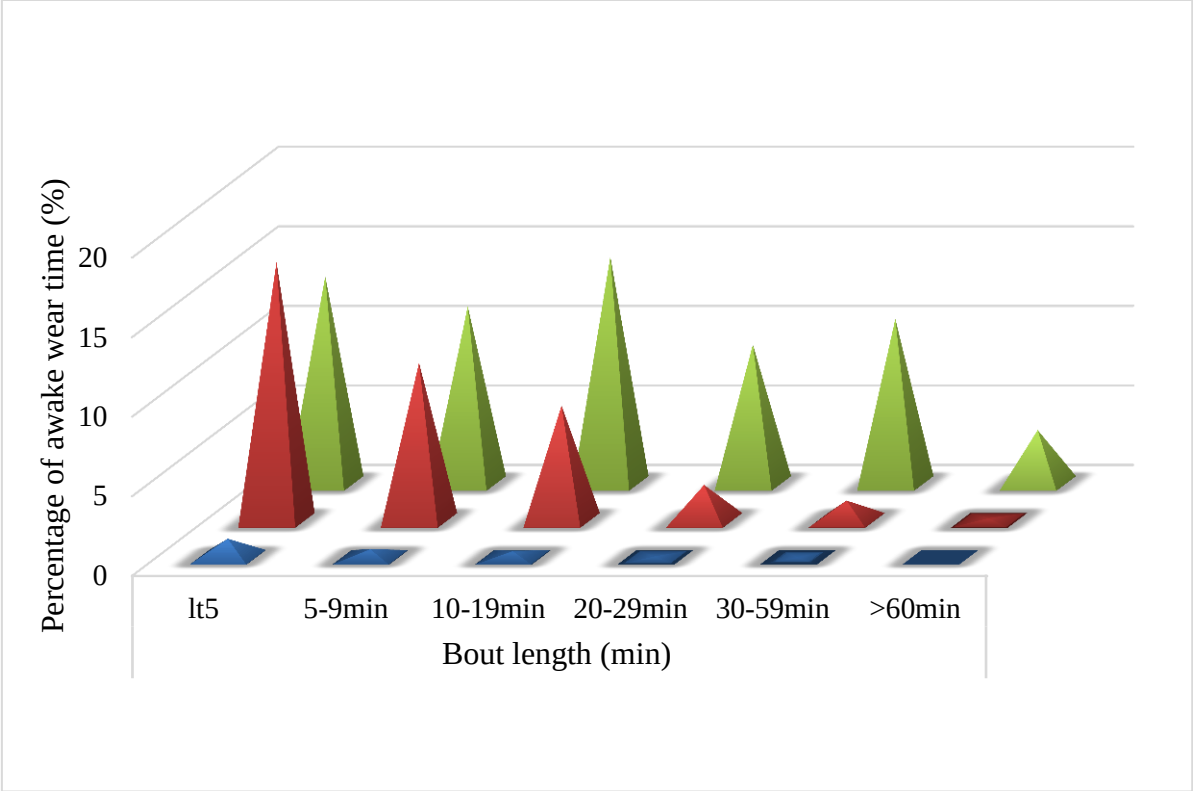

Figure 7 Proportions (%) of the total wake wear time spent in bouts of different lengths (lt = less than) for each of the different intensity activities after 28 weeks of DMARD therapy.

Green bars represent sedentary behaviour (SB), red bars represent light physical activity (LPA) and blue bars represent moderate to vigorous intensity activity (MVPA).

The response to DMARD therapy was measured by the change in DAS scores from baseline to after 28 weeks of DMARD therapy. Not all participants had both baseline and after 28 weeks of DMARD therapy erythrocyte sedimentation rate (ESR) recorded. Therefore in this study treatment response could only be measured in 42 participants.

Figure 9 is a graph demonstrating the mean differences in SB, LPA, MVPA between patients who had good (n=19), moderate (n=12) and no response (n=11) to DMARD therapy. People who had no response to DMARD therapy had the highest increase in time spent in SB (70 min/day) and they also had the greatest decrease in light PA (52 min/day). RA patients with moderate response to DMARD therapy also showed an increase in SB (39 min/day) and a decrease in light PA (18 min/day) after 28 weeks of treatment. Both the no and moderate responders to DMARD therapy had a reduction in the amount of MVPA they performed after 28 weeks (3 min/day and 6 min/day respectively). The participants who had good response to treatment improved in light PA by 11 min/day and their MVPA also improved by 3 min/day. However, none of the results shown in Figure 9 were statistically significant.

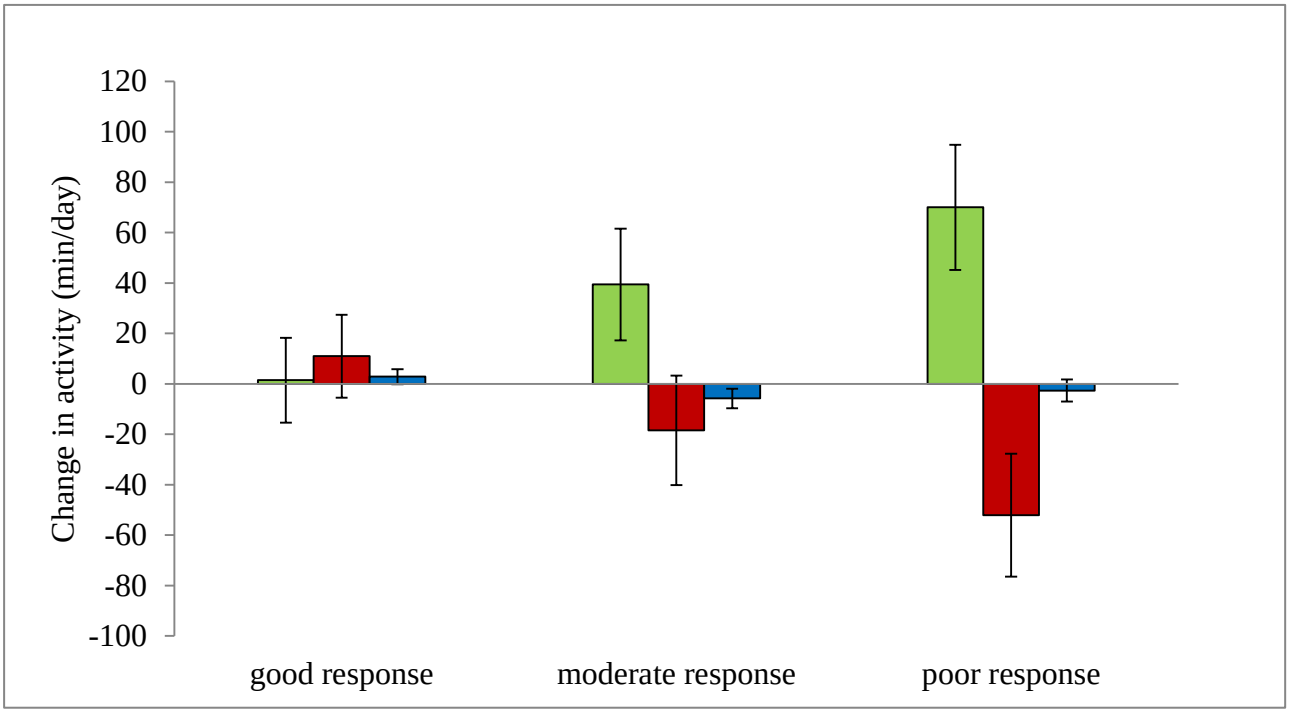

Figure 8 Change in activity behaviours in between patients (min/day) (n=42) with good, moderate or no response to DMARD therapy.

Green bars represent sedentary behaviour, red bars represent light PA and blue bars represent MVPA.

Table 7 shows the patterns of activity behaviours after having divided the patients into groups who showed a good response, a moderate response and no response after DMARD therapy. Those who did not respond to treatment reduced their daily step count by approximately 940 (-2392.5-506.8) steps while those who showed a good response increased their step count by almost 800 (-179.1-1778.4) steps. Again however there were no statistically significant differences between the three groups.

Table 7 The change in sedentary behavior and physical activity means from baseline to 6 month post DMARD therapy between the three groups of rheumatoid arthritis patients who had good (n=19), moderate (n=12) and no (n=11) therapy responses.

	DAS 28 response	Mean change from baseline (95% CI)	p-value
Number of (steps/day)	Good	799.6 (-179.1-1778.4)	0.07
	Moderate	-1106.3 (-2398.2-185.6)	0.07
	No	-942.9 (-2392.5-506.8)	0.15
SB breaks (breaks/day)	Good	1.0 (-4.9-6.9)	0.70
	Moderate	-3.8 (-11.7-4.1)	0.70
	No	-2.5 (-11.3-6.3)	0.90

p-values represent whether the post-value is different to baseline value.

The HAQ scores were also compared between the three patient treatment responses groups. Although not statistically significant, the participants who showed no response to treatment appeared to have the least decrease in HAQ score (Figure 10).

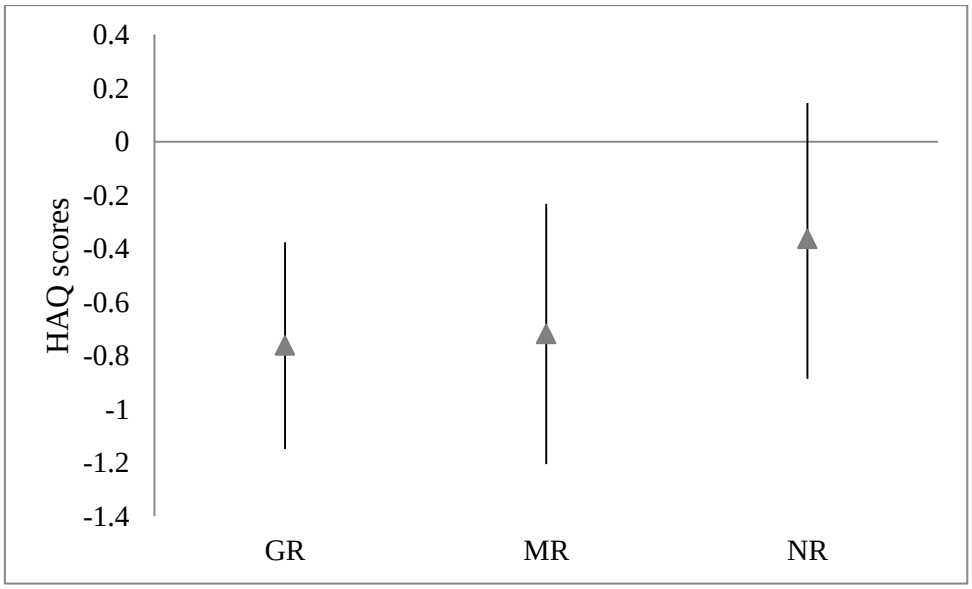

Figure 9 Change in HAQ scores of the good (GR), medium (MR) and no (NR) responders to DMARD therapy.

There were also no significant differences in the change in SF-36 score between the three groups. However unlike with the HAQ scores, participants who showed no response to treatment had the greatest improvement (Figure 11).

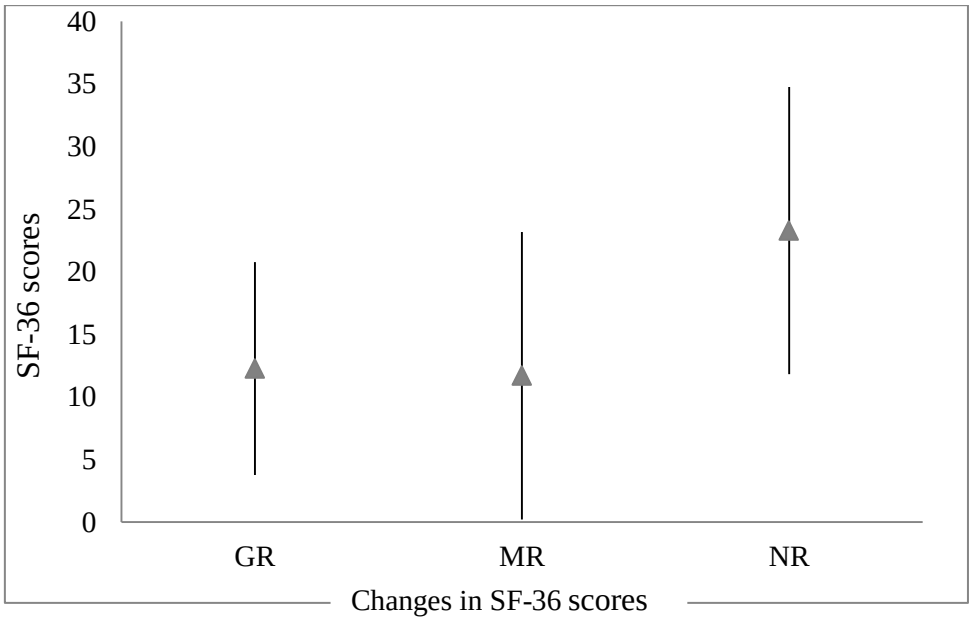

Figure 10 Changes in SF-36 scores of the good (GR), medium (MR) and no (NR) responders to DMARD therapy.

4.4 Markers of bone turnover

Figure 12 shows the difference in the concentration of urinary cross-linked N-telopeptides of type I collagen (NTx) in participants between baseline and after 28 weeks of DMARD therapy. NTx decreased significantly (p=0.01) after 28 weeks of DMARD therapy (median (min and max): baseline: 734 (21.05-2362.15) nmol; 28 weeks: 404 (45.51-2366.00) nmol).

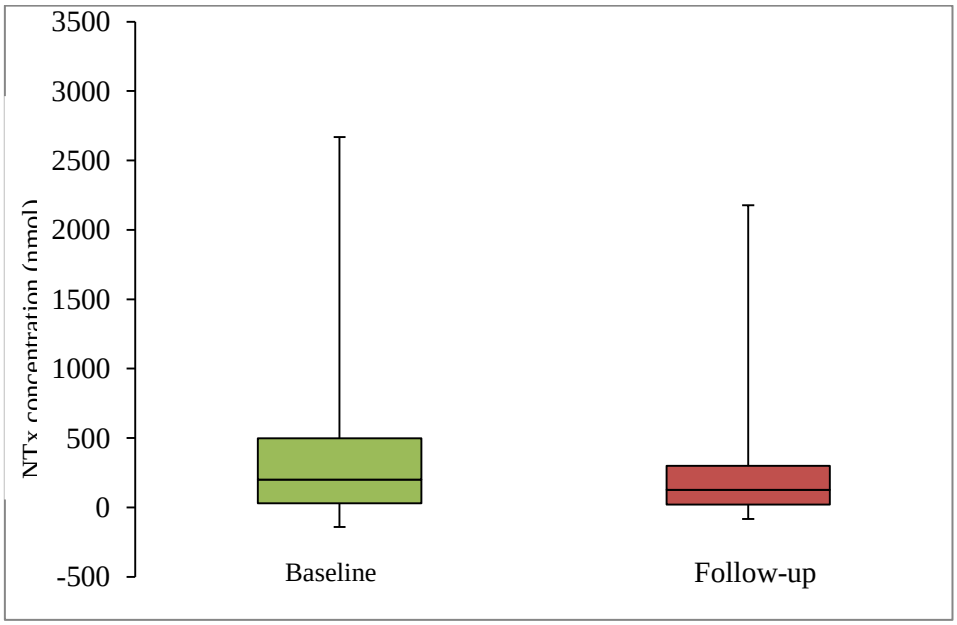

Figure 11 Urinary cross-linked N-telopeptides of type I collagen (NTx) concentration in the RA participants at baseline (green bar) and after 28 weeks of DMARD therapy (red bar).
Data are reported as median.

Figure 13 shows the concentration of serum osteocalcin (OC) before and after 28 weeks of DMARD therapy (median (min-max): baseline: 5.593 (1.15-26.15) ng/mL; post-treatment: 5.139 (1.42-14.39) ng/mL). There was no statistical significance between the osteocalcin concentrations.

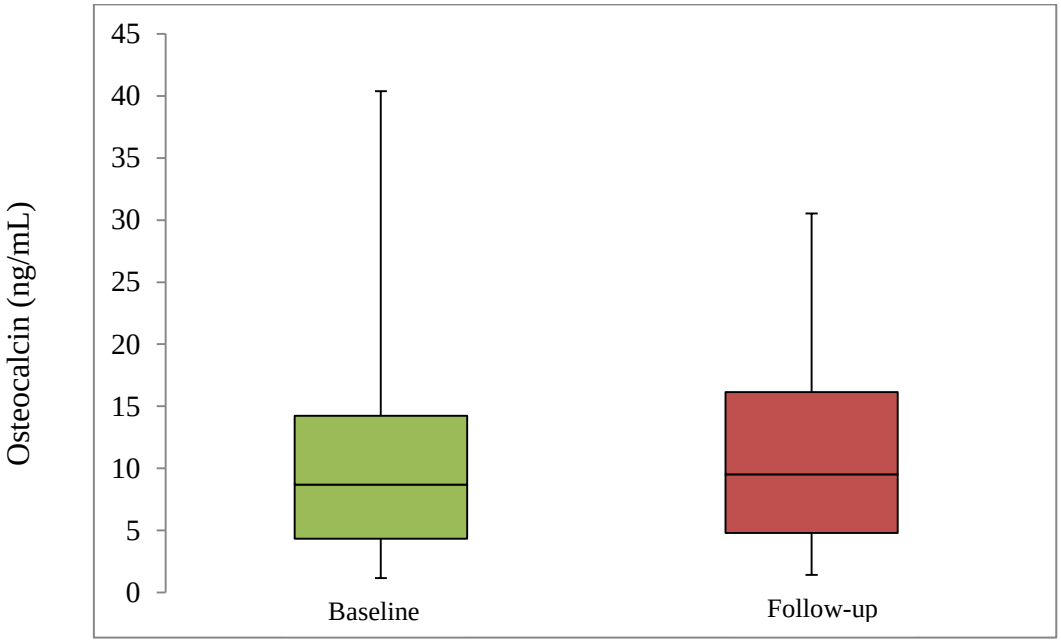

Figure 12 Serum osteocalcin (OC) levels in all participants at baseline and after 28 weeks of DMARD therapy in ng/mL.
Data are reported as median. The green bar represents the baseline osteocalcin data and the red bar represents the osteocalcin data after 28 weeks of DMARD therapy.

Table 8 The relationship between activity behaviours and change in NTx concentration

Model p value	Model R-squared	Parameter	Coefficient	Standard error	p-value
0.19	0.1138	Sedentary behaviour	-20.91	11.93	0.09
		Light physical activity	-24.01	12.62	0.06

Model was adjusted for awake wear time.

Overall there was no significant relationship between the change in the concentration of NTx and change in sedentary or light behaviours ($p>0.05$; Table 8).

Chapter 5: Discussion

This is the one of the first detailed studies to investigate not only total volumes but also the patterns of change in activity behaviours in RA patients (using accelerometers) in low-middle income countries before and after treatment. The current study was carried out in order to measure, describe and investigate the change in subjectively measured functional capacity and objectively measured habitual physical activity (PA) and sedentary behaviour (SB) in participants with rheumatoid arthritis (RA) before and after 28 weeks of initiating drug therapy. Furthermore, the study investigated whether there was a change in bone turnover in participants following treatment and whether there was a relationship between objectively measured patterns of PA and SB and bone health. Overall in this study, objectively measured PA and SB did not change following treatment even though subjective measures of functional capacity did improve. Furthermore, although bone resorption was significantly reduced following treatment, there was no relationship between activity behaviours and bone turnover in this group of patients with RA.

The participants of the current study had poor functional capacity before starting DMARD therapy. The poor functional capacity was reflected by the poor HAQ and SF-36 scores prior to initialization of drug therapy. After 28 weeks of DMARD therapy the HAQ and SF-36 scores improved significantly indicating an improvement in functional capacity. Disease modifying anti-rheumatic drug therapy reduces disease activity by reducing inflammation (Stenger et al., 1998). Inflammation is a main cause of impaired functionality in RA patients. Therefore, initiation of DMARD therapy was effective in improving the functional capacity of the participants in this study.

The results of the current study are consistent with previous studies. Prioreschi et al., (2014a) performed HAQ scoring in 18 newly diagnosed participants at CHBH at baseline and again after three months of DMARD therapy. Prioreschi and colleagues found a significant improvement ($p<0.001$) in the HAQ score of RA diagnosed participants after only three months of DMARD therapy (Prioreschi et al., 2014a). A similar observation was found when Maini et al., (2004) investigated change in functional capacity levels in 428 RA diagnosed UK participants over a period of two years of DMARD therapy. Like in the current study, Maini et al., (2004) found a significant improvement in functional capacity in their RA participants after two years of treatment according to HAQ and SF-36 scores. In addition, the participants in the current study had the most improvement in role

emotional followed by role physical on the SF-36 questionnaire which may suggest that the emotional improvement had a positive influence on how the participants physically felt.

The improvement in functional capacity suggests that the participants perceived themselves to be more physically capable of performing daily habitual activities than they were before treatment. It was expected that an improvement in functional capacity might occur concomitantly with an improvement in habitual activity behaviours. However, in this study the total volume of time spent in LPA, MVPA as well as SB did not change following 28 weeks of DMARD therapy. These findings suggest that an improvement in objectively measured functional capacity following 28 weeks of treatment does not necessarily reflect change in activity behaviour in RA patients. A possible explanation is that questionnaires may be subject to bias and past activities/experiences may be difficult to accurately recall (Terwee et al., 2006), therefore the participants in the current study may have overestimated their ability to perform daily activities of living. Furthermore, the drivers of change in habitual activity and SB may be different to those that drive an improvement in self-perceived functional capacity and a change in one may not necessarily explain a change (or lack thereof) in the other, a topic which warrants further investigation. The participants in this study were not evaluated for their living conditions and lifestyle habits e.g. methods of transportation and type of activities they participate in daily. In addition, for the purpose of this study it was best that the patient not be motivated to increase PA so as to monitor the spontaneity of a change in PA with a reduction in inflammation. It is possible that the above mentioned factors played a role in the resultant lack of change in PA and SB as seen in the current study.

With respect to the patterns of activity behaviours the participants spent almost nine and a half hours of their waking day in SB before they started treatment. Therefore, in addition to low PA levels, participants in the current study spent a large amount of time in SB. After 28 weeks of DMARD therapy the level of SB did not improve and in fact appeared to increase by over 20 minutes per day (although this was not significant). These findings are consistent with previous studies that show that RA patients are highly sedentary even when on DMARD therapy (Paul et al., 2014, Prioreschi et al., 2013).These findings could suggest that, although DMARD therapy slows down disease activity in RA diagnosed participants, (Stenger et al., 1998), it may not reverse joint deformities in this population. If this is the case, RA patients may experience pain relief during treatment but still have

difficulty in moving their joints effectively. The patterns of activity also did not change in these patients following treatment. Participants in the current study spent the greatest proportion of their time in sedentary behaviour in bouts lasting between 10 to 19 minutes both before and after DMARD therapy. Patients with RA need to be aware of trying to minimize the amount of time spent in prolonged periods of sedentary behaviour perhaps by offsetting it with more frequent breaks into light intensity activity. A study performed by Yu et al., (2015) found that RA patients reported less SB and more PA in their questionnaires compared to what the ActiGraph reported (Yu et al., 2015). Therefore similar to what has been suggested for the lack of change in light and moderate intensity activities, the findings of the latter study suggest that subjective methods of measuring progress in RA patients may not be reliable methods of predicting levels of activity behaviours. Another possible explanation for the results in this study is that the participants are indeed capable of increasing their movement levels but decide not to. The RA participants may not move optimally in fear that they might make their condition worse, but interpret their reduced pain on moving as improved functional capacity (Plasqui, 2008). Moreover, RA patients are known to have poor balance and this may cause them to develop fear of falling which leads to reduction in PA levels despite capability (Williams et al., 2010).

The findings of this study differ to the one other study conducted in a similar population. One of such studies was performed on 18 newly diagnosed RA patients from a low-middle income country (Prioreschi et al., 2014a). The study recorded a significant reduction in SB after three months of DMARD therapy. On average LPA did not change in that study, but the 95th percentile of LPA counts (from and Actical accelerometer) improved significantly (Prioreschi et al., 2014a). The differences in results between the current study and that of Prioreschi et al., (2014a) may be explained by the length of time of treatment which differed between the two studies. The participants of the current study were assessed after seven months of DMARD therapy and not three months, as was the case in the study performed by Prioreschi et al., (2014a). Participants may have initially increased their activity behaviours after a shorter time period, however this was not assessed, and then perhaps they tended to go back to baseline levels of activity once being on treatment for a longer period of time. This reason would support the fact as mentioned above that drivers of activity change are not solely due to pain and inflammation alleviation. In addition, after 4 months of DMARD therapy, the rheumatologists at CHBAH may adjust the therapy of

RA patients in an attempt to improve the response to treatment if the patients are not showing satisfactory improvements in disease activity. Therefore in my study at any given time point the treatment period, there were patients who responded well to treatment as soon as it was initiated, after the first adjustment of therapy but then there were also those patients who did not respond well to treatment. Due to some patients having had an improvement in disease activity for longer than others may have been the main reason why overall activity behaviours did not change over the total seven month period. In the Prioreschi study, it was not reported whether there were patients who responded well or not to treatment.

Light intensity PA was mostly performed in bouts lasting less than five minutes at a time and there was no difference in the proportion of time spent engaged in LPA during the day before and after treatment. However, prior to and following 28 weeks of DMARD therapy the participants took part in approximately 17 and 22 minutes of MVPA per day respectively. Again, patterns of MVPA, (as measured by bouts of activity during the day) did not change significantly after treatment. The fact that participants spent that much time in MVPA may mean that they were already performing at their capacity for physical activity and were not able to increase their activity anymore. Although not significant, a five minute increase in MVPA is certainly notable. These levels of MVPA may also explain the difference in improvement between objectively measured activities and subjectively measured functional capacity. Similar levels of MVPA have been shown in RA patients in a study in the USA (approximately 19 minutes per day) (Gilbert et al., 2018) and even when these participants were motivated to increase physical activity levels (through the use of motivational counselling) they did not change their MVPA levels (Gilbert et al., 2018). However, the participants in the above study had less frequent contact with their PA advocate compared to participants in studies that showed improvement in PA with motivation. The participants in the current study were not motivated to increase their PA levels so as to influence their results (Gilbert et al., 2018). Moderate to vigorous PA involves activities that result in a noticeable increase in heart rate such as brisk walking, gardening or running (Moore et al., 2012). The findings from this and other studies suggest that motivations other than a decrease in self-perceived pain and function may be responsible for a change in habitual activity behaviours.

Only 39% of all participants in the present study reached PA levels recommended by global PA guidelines of 150 mins of MVPA per week, after 28 weeks of treatment. The

percentage of RA patients in this study who reach PA levels recommended by WHO are higher than that of a healthy Canadian population (17% men and 14% women) (Colley et al., 2011). However, the participants in the current study who met the PA guidelines, unlike the Canadian population, did not perform MVPA for at least 10 minutes at a time as recommended by current global PA guidelines. Nevertheless, the new physical activity guideline report stated that it may not be correct to say that PA performed in duration less than 10 minutes at a time is of no health benefits as suggested by the latest PA guidelines (King et al., 2018).

It would appear that there is currently no literature on the prevalence of RA patients who reach PA levels as recommended by global guidelines according to objective measurements in low-middle income countries. Similar to the findings in the present study, a study performed in USA showed that only 38.3% of people diagnosed with either osteoarthritis or RA reported meeting the global PA guidelines as recommended by WHO (Fontaine et al., 2004). Due to the nature of the disease it is understandable that patients with mobility disorders fail to adequately meet the recommended doses of physical activity. However as mentioned above, these participants were seemingly more physically active compared to RA patients (Gilbert et al., 2018). The types of activity that require a moderate to vigorous effort are most often obtained during the performance of structured exercise and the patients in this sample may not have subscribed to that type of physical activity. Furthermore it may be that a reduction in pain and improvement in joint movement is more related to an improvement in quality of life rather than a change in the habitual daily activities that one takes part in let alone the amount of moderate-vigorous activity one takes part in. A more feasible target of change may be the amount of LPA that patients perform and more controlled trials are needed in future in these patient populations to validate this proposal.

The patients in this study also did not walk more after treatment despite reporting that they felt more capable to do so. These results are in line with the fact that LPA and MVPA, which include slow and brisk walking, did not change after treatment. Grondal et al., (2008) found that 80% of their participants complained about difficulty in walking (Grondal et al., 2008). The latter study also explained that since RA is known to frequently reduce the range of motion (ROM) of foot joints, RA sufferers find it difficult to walk (Grondal et al., 2008). This could suggest that 28 weeks of DMARD does not improve the ROM of foot joints. However, ROM was not measured in this study. Therefore, although

DMARDS not improving ROM is a possible explanation for no improvement in step count, this explanation is not conclusive.

The participants in the current study were therefore further divided into three groups for analysis based on whether they had a good, moderate or no response to DMARD therapy. When looking at the subjective measures of activity behaviours, participants who had a good response to DMARD therapy did not change their activity behaviours greatly while those who had no response to treatment had the greatest increase in SB (approximately 70 minutes per day) and the greatest decrease in LPA (approximately 52 minutes per day). Furthermore, participants with no response to treatment tended to take fewer steps (940 less steps per day) after treatment, while those with good response tended to improve their step count by 800 steps per day after treatment. These results suggest that the better a person with RA responds to DMARD the more improved their habitual PA levels may be. Future studies should recognize the importance of using objective methods of assessment (both the DAS and accelerometers) in measuring functional capacity in RA patients and these results further strengthen the argument that the objective response to DMARD therapy may be related to changes in habitual activity behaviours in RA patients preferentially over the subjective/self-reported improvements in functional capacity. However, it must be noted that there were no statistically significant differences in the activity behaviour levels between the three groups of the responders to treatment. Yet a 70 minute increase in SB in a population that is already greatly sedentary, may compound the co-morbidities generally experienced by people with RA.

It is important however, to bear in mind that the analysis showed no significant differences in degree of improvement in functional capacity, according to HAQ and SF-36, between the three groups. These findings mean that participants who responded well to treatment improved their functional capacity no differently to participants who responded moderately or poorly to treatment after 28 weeks of being on DMARD therapy. Although the changes were not statistically significant, participants with no response to treatment showed the least improvement in HAQ functional ability score but the greatest improvement in health-related quality of life, according to SF-36, compared to participants with good and moderate response to treatment. It is unclear as to why the improvement in functional capacity of the group with lower disease activity would be less than the improvement in functional capacity of the group that had higher disease activity. It is important to keep in mind that SF-36 and HAQ are both subjective measurements while

DAS is objectively measured. Therefore, although DAS showed an accurate measure of a lower improvement in the disease activity of the no-response group, the participants may have not have been accurate in answering the questions of SF-36 of HAQ, possibly again due to the issue of subject bias regarding recall.

To understand the differences in the changes in patterns of PA in RA patients who responded well, moderately and poorly to DMARD requires a better understanding of why participants who were diagnosed with RA around the same time and were given the same treatment would have different treatment response after 28 weeks of treatment. Hider et al., (2005) conducted a systematic review and found that there are a number of factors that appear to be indicators of how responsive a RA patient will be to anti-rheumatic drug therapy (Hider et al., 2005). Being female and having an early onset of RA increases the likelihood of a no response to DMARD therapy (Hider et al., 2005). There were indeed more females than males in this study however disease duration was not measured and therefore it is not possible to say whether diagnosis delay was the case in this study. RA patients diagnosed and initiated on DMARD therapy at least within a few months of developing RA have a good prognosis compared to those diagnosed later (Nell et al., 2005). Longer disease duration may mean that the inflammation gets a longer time to damage the joints (Nell et al., 2005). However, in the current study disease duration was not noted. Therefore, this explanation is not certain.

Interestingly, NTx concentration which is indicative of bone resorption was significantly reduced after 28 weeks of DMARD therapy. This finding suggests that there was reduced bone loss following therapy. However there was no difference in the concentration of the bone formation marker, osteocalcin following treatment therefore the overall interpretation of the changes in bone turnover in this sample of patients remains not well delineated. The finding of the change in NTx concentration following DMARD therapy is similar to that of another study. However one that was of longer duration than my study. In 26 female and 25 male participants diagnosed with active RA, the study showed that bone resorption markers were reduced after two years of DMARD therapy (Dolan et al., 2002). In addition, overall there was no relationship between the change in bone resorption and the changes in either sedentary behaviour or light activity in these patients. Considering that the objective measures of PA did not change after 28 weeks of DMARD therapy, reduced bone loss may be as a result of the reduced hyper-inflammation that erodes bone at the joints as opposed to increase a change in activity behaviours. The participants' in the current study also used

low doses of glucocorticoids (10mL of prednisone) to manage their RA. Low doses of glucocorticoids significantly retard bone joint erosion, and as a result bone loss is reduced (Bijlsma et al., 2002). A longer follow-up period may be needed to conclusively establish whether activity behaviours indeed have a role to play in maintenance of bone health in RA patients over and above their treatment regime. Furthermore other co-morbidities influenced by physical activity and sedentary behaviours and that may afflict RA patients should be investigated in relation to the activity behaviours themselves. These studies will further increase our understanding of the role of activity behaviours in maintaining the health and quality of life in patients with mobility disorders.

Limitations

There are some limitations to the study that require consideration. The HAQ and SF-36 used to score RA patients at CHBAH is written in English. It is then translated by a nurse if the RA patient does not understand English or if she/he is illiterate. South Africa has 11 official languages. Our study consisted of Tsonga, Zulu, English, Afrikaans and Sotho speakers. The interpretation of the questions in the HAQ and SF-36 scores may have been difficult for the patients due to the language diversity at CHBAH although the nurses did their best to translate and have experience in translating the questionnaires into the first language of the participants.

The difference in the time spent on treatment that was effective for each participant may have played a big role in the results that are seen this study. Dividing the sample into three groups of responders to treatment for analysis could then also have reduced the power of the study (by reducing the sample size) and may then be a reason why there was no statistical difference between the three groups. The high dropout rate and the fact that some of the accelerometer readings did not have sufficient wear time for the data to be included as valid, also reduced the size of the sample at follow-up. Furthermore, we used traditional cut points for activity thresholds which were developed on healthy populations, since no such guidelines for people with RA exist as yet.

It is possible that some of the participants had a reduced joint space which could have contributed to a reduced ROM. However, in the current study no assessment was performed to adjust for this in the current analyses. Some of the factors that affect bone health such as diet, social habits, menopause and occupation were also not assessed and adjusted for in the analysis although these factors may be considered as confounders to

bone health. However because this was a follow up study each participant was their own control and provided that they did not change their health habits much (apart from the DMARD therapy) this should not have been a major limitation.

Due to the working schedule the participants of the current study had to be seen by four different rheumatologists. Therefore the method of management may have been different. The rheumatologists did not all order Erythrocyte Sedimentation Rate (ESR) blood tests at the same time. Therefore, some participants had 28 week DAS scores whiles others did not, reducing data. The DMARD therapy was also prescribed according to patient response throughout the weeks. Therefore each participant had a unique drug therapy to them.

Disease duration was not observed in the current study, which may have helped shed light on the reasoning behind the difference in DMARD response as mentioned above.

The lack of motivation to improve PA may have been the reason why there was no change in PA.

The dietary intake of the participants in this study was not assessed and could have contributed towards bone health.

Chapter 6: Conclusions

Participants in the current study reported an improvement in self-reported functional capacity after 28 weeks of DMARD therapy as reflected in the HAQ and SF-36 scores. Patients with RA from a low-middle income country appear to live physically inactive and sedentary lifestyles as evidenced by the accelerometry data in this study have a difficult time in meeting PA levels recommended by WHO guidelines. This study suggests that SF-36 and HAQ is not necessarily indicative of PA and SB levels in RA patients, but rather how well a patient feels during drug treatment. A combination of questionnaires scores and accelerometer readings could give a more holistic picture of the patient's progress during treatment. A more holistic picture of the patient outcome during drug therapy may assist in better management of RA in health care centers.

The patterns of accumulation of SB and LPA also did not change significantly following treatment. The study highlights the role that objectively assessed PA and SB patterns could play in understanding activity behaviours of patients with RA although trials with longer follow-up times are required in future studies. Understanding the reasons behind the patterns of SB and PA accumulation in this population can contribute towards developing guidelines that assist those who suffer from RA to offset their sedentary time with light physical activity. The participants in the current study performed mostly light PA. Light PA is beneficial for maintaining health and well-being (Buman et al., 2010). Therefore, breaking up SB with light PA can be beneficial for a population that struggles to perform MVPA such as RA patients. A deliberate attempt to manipulate the pattern of accumulation of SB by means of a structured guideline may prove beneficial to those with RA. Such an approach can be easier to follow for people with musculoskeletal conditions such as RA as opposed to trying to keep up with PA guidelines as recommended by WHO. It is important to consider however, how the patient responded to treatment as this may determine the ability of the patient to additionally modify their activity behaviours.

The current study also showed a reduction in bone loss after treatment but there was no relationship between bone health and activity behaviours in these patients. Perhaps with motivation and clear guidelines RA patients can live a more active lifestyle which will improve their bone health and improve their quality of life. This study can contribute towards better understanding the reason why RA patients behave the way they do. Further

studies that investigate the implications of PA guidelines that aim to improve PA and increase breaks between SB are necessary.

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Appendix-A

R14/49 Dr Rebecca Meiring et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150741

NAME: (Principal Investigator)	Dr Rebecca Meiring et al
DEPARTMENT:	School of Physiotherapy Division of Rheumatology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	An Investigation into the Relationship between Disease Activity, Bone Turnover Markers and Physical Activity in Patients with Rheumatoid Arthritis
DATE CONSIDERED:	31/07/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	18/09/2015

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

R14/49 Miss Nonhlanhla Mthembu et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170296

NAME: (Principal Investigator)	Miss Nonhlanhla Mthembu et al
DEPARTMENT:	Physiology School of Physiology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	An Investigation into the Relationship between Disease Activity, Bone Turnover Markers and Physical Activity in Patients with Rheumatoid Arthritis
DATE CONSIDERED:	Adhoc
DECISION:	Approved unconditionally
CONDITIONS:	Sub-Study (M150741)
SUPERVISOR:	Dr Rebecca Meiring
APPROVED BY:	Professor P. Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	13/03/2017

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 Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised 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 to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in February and will therefore be due in the month of February each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix-B

CONSENT TO ACT AS PARTICIPANT IN RESEARCH

I, _____(full name and surname) agree to participate in the study titled: **Assessment of bone turnover in patients with rheumatoid arthritis**.

The procedures/questionnaires have been explained to me and I understand and appreciate their purpose, any risks involved, and the extent of my involvement. I have read and understand the attached information sheet.

I understand that the procedures form part of a research project and may not provide any direct benefit to me.

I understand that all experimental procedures have been sanctioned by the Committee for Research on Human Subjects, University of the Witwatersrand, Johannesburg.

I understand that my participation is voluntary and that I am free to withdraw my participation from the project at any time without prejudice.

_____ _____

Participant name and signature Date

_____ _____

Investigator name and signature Date

Appendix-C

GENERAL HEALTH QUESTIONNAIRE

We would like to know about your health. Please answer the questions below as accurately as possible. This questionnaire may be filled out electronically or you can fill it out by hand. If you fill it in electronically, to tick a box, double click the box and under default value select the checked option. Click ok. If you need to type, click in the box provided and write as much as is needed.
Thank you very much.

1) Compared to other adults your age, how would you rate your health in the last TWO years? Please tick one box.

Better than others	☐	Worse than others	☐
Same as others	☐	Much worse than others	☐

*2) **In the last TWO years:***

a) Have you gone to hospital? Yes ☐ No ☐

*b) If **yes**, what did you go to hospital for?*

c) How long did you stay in hospital for?

d) Have you had any surgical procedures in the last year? Yes ☐ No ☐

If yes, which procedure did you have?

3) Please tick any illnesses that you may have currently or have had in the last SIX months.

Illness		**How long ago?**	**Fully recovered?**
Heart attack, stroke	☐	_____	Yes ☐
No ☐			
Diabetes Mellitus Type I	☐	_____	Yes ☐
No ☐			
Diabetes Mellitus Type II	☐	_____	Yes ☐
No ☐			
Cold	☐	_____	Yes ☐
No ☐			
Influenza ('Flu)	☐	_____	Yes ☐
No ☐			
High total cholesterol	☐	_____	Yes ☐
No ☐			
None	☐		

4) Please write down any medication/treatment that you may be on or have taken in the last SIX months.

5) Do you smoke?

Yes ☐ No ☐

6) Please tick the box of the items that you own:

☐ Microwave	☐ Telephone – Landline	☐ Cell phone
☐ DSTV, Top TV	☐ Car How many?	☐ Formal housing
☐ Washing machine	☐ Fridge	☐ Indoor toilet
☐ Indoor water	☐ Video machine/DVD player	☐ Television
☐ Electricity	☐ Dishwasher	☐ Computer

☐ How many adults (over 18) in your family?

Highest level of education?

_____

THANK YOU FOR TAKING THE TIME TO COMPLETE THIS QUESTIONNAIRE

Appendix-D

Medical Outcomes Study Questionnaire Short Form 36 Health Survey

This survey 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. Thank you for completing this survey! For each of the following questions, please circle the number that best describes your answer.

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,	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	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?
(Circle One Number on Each Line)

	Yes, Limited a Lot (1)	**Yes, Limited a Little (2)**	**No, Not limited at All (3)**
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3

g. Walking **more than a mile**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dressing yourself	1	2	3

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**?
(Circle One Number on Each Line)

	Yes (1)	**No (2)**
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 (for example, 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 any emotional problems** (such as feeling depressed or anxious)?
(Circle One Number on Each Line)

	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

These questions are about 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. **(Circle One Number on Each Line)**

9. 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

	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
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.)? (Circle One Number)	
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

11. How TRUE or FALSE is each of the following statements for you. (Circle One Number on Each Line)

	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 as 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

Appendix-E

Enter clinical data to calculate the Disease Activity Score

DAS28 Calculator v1.1-beta

for the DAS28 with 4 variables

by Alfons & Michiel

Clinical variable	Value
tender joint count (0-28)	0
swollen joint count (0-28)	0
ESR (mm/hr)	0
VAS general health patient (mm)	0

input is not between 1 and 300

DAS28	#NUM!

Excel document available at:

https://www.das-score.nl/das28/DAScalculators/dasculators.xls