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Obesity, weight change and disease activity measures in patients with rheumatoid arthritis

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Boston University
OBESITY, WEIGHT CHANGE AND DISEASE ACTIVITY MEASURES
IN PATIENTS WITH RHEUMATOID ARTHRITIS

by

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OBESITY, WEIGHT CHANGE AND DISEASE ACTIVITY MEASURES IN PATIENTS WITH RHEUMATOID ARTHRITIS

DAVID JOSEPH KREPS

ABSTRACT

Background: Rheumatoid arthritis (RA) is an autoimmune disease that causes inflammatory polyarthritis, typically of the small joints. Obesity, a serious global epidemic, has been shown to increase systemic inflammatory biomarkers, several of which are related to RA pathophysiology. Associations have been observed between obesity and worsened RA disease activity outcomes in cross-sectional studies. Limited longitudinal studies investigated the effects of weight change on RA disease activity measures. Surgical interventions for weight loss in RA patients showed marked improvement in RA disease activity measures and outcomes but typical weight change in a clinical setting has not been investigated.

Objective: To investigate the impact of typical weight change on RA disease activity measures.

Methods: We conducted a retrospective cohort study on 178 RA patients seen in typical clinical practice that met the inclusion criteria for the study, which included patients with a minimum of two clinical disease activity assessments (CDAI) with corresponding body mass index (BMI) measures. Medical record review was
conducted for each clinic visit where CDAI and BMI were measured, and at each of these visits, sociodemographic, lifestyle, medication usage, questionnaire data, RA characteristics, laboratory values, and comorbidities were collected. Linear regression was used to analyze the association between ΔBMI and ΔCDAI, defined at the dates of minimum and maximum BMI for each subject, adjusting for confounders including sex, age, disease duration, smoking status, serologic status, and steroid usage. Logistic regression was performed to evaluate whether ΔBMI was associated with low/remission RA disease activity according to accepted CDAI cutoffs.

**Results:** Unadjusted linear regression was performed on all 178 subjects to analyze the overall trend within the sample population. For every 1 kg/m² increase in BMI, CDAI increased by 0.49 points, but these results were not statistically significant (p=0.155, 95%CI -0.176, 1.097). Subjects were stratified into BMI gain, stable, and loss groups. Within the BMI loss group (defined as those whose BMI decreased by more than 1 kg/m²), a significant association was found with ΔCDAI (β=-2.61 [p=0.028, 95%CI -4.91, -0.298]). Unadjusted linear regression on the BMI gain and stable groups was found to be not statistically significant. This association remained significant after adjusting for sex, age, disease duration, smoking status, serologic status, and steroid usage (β=-2.499 [p=0.044, 95%CI -4.94, -0.061]). There was no association between ΔBMI and low/remission RA disease activity (OR 0.990, 95%CI 0.855, 1.146). When
stratified by BMI gain, stable, and loss groups there was no significant association with low/remission RA disease activity.

**Conclusion:** These results suggest that weight loss may be associated with improved disease activity among patients with RA seen in a typical clinical setting. Weight loss has the potential to be a non-pharmacologic intervention to improve RA disease activity. Prospective studies of weight loss and RA disease activity are necessary to replicate these results.
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<td>ACPA</td>
<td>Anti-cyclic citrullinated protein antibody</td>
</tr>
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<td>ACR</td>
<td>American College of Rheumatology</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>BRASS</td>
<td>Brigham Rheumatoid Arthritis Sequential Study</td>
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<tr>
<td>CDAI</td>
<td>Clinical Disease Activity Index</td>
</tr>
<tr>
<td>CI</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>CORRONA</td>
<td>Consortium of Rheumatology Researchers of North America</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>DAS28</td>
<td>Disease Activity Score with 28 joints</td>
</tr>
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<td>DMARDs</td>
<td>Disease-modifying antirheumatic drugs</td>
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<tr>
<td>EMR</td>
<td>Electronic medical record</td>
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<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>EULAR</td>
<td>European League Against Rheumatism</td>
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<td>GERD</td>
<td>Gastrointestinal Reflux Disease</td>
</tr>
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<td>HR</td>
<td>Hazard ratio</td>
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<td>IL</td>
<td>Interleukin</td>
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<td>ILD</td>
<td>Interstitial lung disease</td>
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<td>MCP</td>
<td>Metacarpophalangeal joints</td>
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<tr>
<td>MCSF</td>
<td>Macrophage Colony Stimulation Factor</td>
</tr>
<tr>
<td>MHAQ</td>
<td>Modified health assessment questionnaire</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
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</table>
OR .......................................................... Odds ratio
PAS .......................................................... Patient activity scale
PIP .......................................................... Proximal interphalangeal joints
RA .......................................................... Rheumatoid arthritis
RANK ....................................................... Receptor Activator of Nuclear Factor Kappa β
RANKL .................................................... Receptor Activator of Nuclear Factor Kappa β Ligand
RAPID-3 .................................................... Routine Assessment of Patient Index Data
RF .......................................................... Rheumatoid factor
SDAI ........................................................ Simple disease activity index
SJC .......................................................... Swollen joint count
TJC .......................................................... Tender joint count
TNF-α ....................................................... Tumor necrosis factor-α
VAS ........................................................ Visual analog scale
WHO ........................................................ World Health Organization
INTRODUCTION

Rheumatoid arthritis (RA) is a disease currently affecting 1.5 million Americans, with 41 out of 100,000 people developing the disease annually [1]. RA accounts for 22% of all the deaths due to arthritis [2, 3]. Patients with RA have significant disability; RA patients are 30% more likely to need help with personal care and twice as likely to have health-related activity limitation compared to people without RA [4]. Due to this burden, RA is expensive for patients, employers, family members, and governments—responsible for $39.2 billion annual lost revenue [5].

Biology of RA

RA is an autoimmune disease that causes an inflammatory polyarthritis and most commonly affects the small joints of the hands and feet. There are several extra-articular organ systems affected by RA in addition to systemic effect [6]. The precise cause of RA manifestation remains unknown, but the pathogenesis and pathology of RA likely involve several complex immune pathways [6, 7]. These pathways, outlined in Figure 1, likely interact differently in patients making a single causative factor for RA still difficult to determine.
Figure 1: Current views on pathogenesis of rheumatoid arthritis.
Arrows show some of many interactions in rheumatoid arthritis pathogenesis. Schematic depiction of events presumably occurring in synovial membrane, as well as articular cartilage and subchondral bone, which are surrounded by aggressive rheumatoid synovitis. Blys=T lymphocyte stimulator. C=complement. CP=crystalline peptide. CR=complement receptor. FcR=Fc receptor for the Fc portion of IgG. IC=immune complex. IFN=interferon. IFNγ=type 1 interferons. IL=interleukin. RF=rheumatoid factor. TACI=transmembrane activator and calcium modulator and cyclophilin ligand interactor. TCR=T-cell receptor. Th1=T-helper 1 cell. TLR=Toll-like receptor. Treg=regulatory T cell.

Figure 1. Overview of the biologic pathways involved in RA pathogenesis (Taken from [7]).
Generally, CD4+ T cells become activated after stimulation of a still undetermined antigen, perhaps elicited in genetically susceptible individuals after environmental factors, such as cigarette smoking or infection. These cells stimulate other immune and inflammatory cells and pathways, including the activation of cytokines, macrophages, and antibody-producing B cells [8].

The major pro-inflammatory cytokines that are activated include Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), IL-7, IL-17 and vascular endothelial growth factor (VEGF). These pro-inflammatory cytokines cause numerous local and systemic effects that are outlined in table 1 [6]. All of these effects further amplify the inflammatory response occurring within the joints.

Activated B cells are responsible for the production of autoantibodies related to RA. The two most commonly found antibodies in RA are rheumatoid factor (RF) and anti- citrullinated protein antibody (ACPA). If either antibody is present, a patient is referred to as having “seropositive RA.” However, about one-third of patients with RA do not have detectable autoantibodies (termed “seronegative RA”) [7]. Other autoantibodies have been detected on research assays, but RF and ACPA are currently the only autoantibodies used clinically. Patients with RA do not typically acquire or lose RF or ACPA after diagnosis. Therefore, these tests are most helpful in diagnosis of RA and do not help measure disease activity. However, patients with seropositive RA typically have a more severe disease course, such as bone erosions, disability, extra-articular manifestations, and ongoing inflammation [9-11].
As RA progresses, the CD4+ T cells recruit macrophages furthering the autoimmune process. The macrophages in turn upregulate osteoclasts to the synovial membrane, which destroys bone and leads to joint erosions and pathologic pannus formation. This process is mediated by macrophage colony

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<th>Cytokine</th>
<th>Role in the disease process</th>
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<td>TNF-α</td>
<td>Local effects: increased monocyte activation, cytokine release, PG release; T-cell apoptosis, clonal regulation, TCR dysfunction; increased endothelial cell adhesion molecule expression, cytokine release; decreased synovial fibroblast proliferation, collagen synthesis; increased MMP and cytokine release. Systemic effects: acute-phase protein production, HPA axis dysregulation (fatigue and depression); CVD promotion.</td>
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<tr>
<td>IL-6</td>
<td>Local effects: osteoclast activation, neutrophil recruitment, pannus formation via promotion of VEGF production, B-cell proliferation and antibody production, T-cell proliferation and differentiation. Systemic effects: acute-phase protein production, anemia (via heparin production); CVD promotion; osteoporosis; HPA axis dysregulation (fatigue and depression).</td>
</tr>
<tr>
<td>IL-1</td>
<td>Local effects: increased synovial fibroblast cytokine, chemokine, MMP and PG release; increased monocyte cytokine, reactive oxygen intermediate and PG release; osteoclast activation; endothelial cell adhesion molecule expression. Systemic effects: acute-phase protein production; CVD promotion; HPA axis dysregulation (fatigue and depression).</td>
</tr>
<tr>
<td>IL-17</td>
<td>Recruitment of monocytes and neutrophils by increasing local chemokine production; facilitation of T-cell infiltration and activation; amplification of immune response (e.g. by induction of IL-6 production); increased synovial fibroblast cytokine and MMP release; osteoclastogenesis [30] and cartilage damage.</td>
</tr>
<tr>
<td>VEGF</td>
<td>Angiogenesis, contributing to pannus formation.</td>
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Table 1: Outline of the major cytokines that play a role in RA disease pathogenesis (Taken from [6]).
stimulation factor (MCSF) and the interaction of the receptor activator of nuclear factor kappa β (RANK) and RANK ligand (RANKL) [12]. Joint destruction is further enhanced by enzymes secreted by neutrophils, synoviocytes, and chondrocytes [7].

Several hallmark deformities have been described as being caused by RA due to bone and cartilage destruction. These include Boutonnière’s deformity, swan-neck deformity, hitchhiker’s thumb, and claw toe deformity [13]. Presence of these deformities is a marker of clinically advanced RA and is associated with increased morbidity and mortality.

All of these complex pathways of inflammation cause elevation of serum inflammatory markers, such as erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) during flares of RA such as synovitis in the small joints of the hands and feet [14]. ESR, a non-specific inflammatory marker, measures the rate at which red blood cells settle in one hour. CRP, another nonspecific inflammatory marker, is a protein that increases with inflammation in the body. Both of these blood tests are used clinically to detect active inflammation in a RA patient. However, flares and active disease may occur even with normal serum inflammatory markers, emphasizing the need to integrate other components to measure RA disease activity [14].

**Classification of RA**

Due to the complex nature of RA pathophysiology and unique manifestation and presentation of each RA patient, the American College of
Rheumatology (ACR) created sets of criteria to define RA and in doing so have 
created a benchmark to standardize patients included in RA research studies. 
These criteria also help differentiate RA from a number of diseases with similar 
symptoms but separate disease pathogenesis. These include the 1987 ACR and 
2010 ACR/EULAR criteria. The 1987 ACR criteria for the classification of RA, 
utilized clinical data and streamlined defining RA to having a minimum of 4 of 7 
criteria for at least 6 weeks in duration [15]. These criteria include: morning 
stiffness over an hour, arthritis of 3 or more joint areas, arthritis of hand joints, 
symmetric joint involvement, rheumatoid nodules, presence of rheumatoid factor in the serum, and radiographic changes such as erosions or periarticular 
osteopenia [15]. The combination of these criteria were chosen to optimize the 
specificity, selectivity, and overall accuracy of identifying a homogeneous 
phenotype of RA patients for use in research studies [15].

With advancements in scientific research for RA, the ACR and the 
European League Against Rheumatism (EULAR) created a new set of RA 
classification criteria in 2010. This criteria overhaul was mainly due to criticism 
that the 1987 criteria was not specific in detecting patients with early RA that did 
not have end-stage changes such as rheumatoid nodules and bone erosions. In 
addition, the 1987 criteria did not include ACPA testing which was described in 
the late 1990s to be much more specific than RF for diagnosing RA [16]. The 
2010 criteria include the number and type of joints involved, RA-related 
autoantibodies of RF and ACPA, acute phase reactants of ESR and CRP,
symptom duration, and uses a scoring system where a patient must score at least 6 out of 10 to be defined as having RA [16]. Both criteria exclude patients diagnosed with similar but separate diseases, such as psoriatic arthritis, systemic lupus erythematosus, and reactive arthritis.

In comparing the 1987 and 2010 criteria, both have strengths and limitations. The 2010 is more sensitive in detecting patients with early RA but undifferentiated forms of inflammatory arthritis may be incorrectly classified as RA when they later may develop another definable disease such as lupus, reactive arthritis, or psoriatic arthritis. The 1987 criteria has the opposite quality where patients with early RA may not be classified as RA despite significant joint involvement, disability, and pain [17]. Further, many options for RA treatment now exist and research suggests that the optimal time to initiate aggressive treatment is in the early phase of the disease in order to prevent late-stage findings such as erosions, nodules, and deformities and thus improve the long—term quality of life and prevent disability for RA patients. Due to these opposing factors, both criteria are still used for research purposes. The 1987 and 2010 criteria can be found outlined in Tables 2 & 3.
Table 2: 1987 ACR criteria for RA classification. Patients need at least 4 out of 7 criteria to be considered as having RA (Taken from [15]).

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<th>Definition</th>
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<tr>
<td>1. Morning stiffness</td>
<td>Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement</td>
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<td>2. Arthritis of 3 or more joint areas</td>
<td>At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints</td>
</tr>
<tr>
<td>3. Arthritis of hand joints</td>
<td>At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint</td>
</tr>
<tr>
<td>4. Symmetric arthritis</td>
<td>Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)</td>
</tr>
<tr>
<td>5. Rheumatoid nodules</td>
<td>Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician</td>
</tr>
<tr>
<td>6. Serum rheumatoid factor</td>
<td>Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in &lt;5% of normal control subjects</td>
</tr>
<tr>
<td>7. Radiographic changes</td>
<td>Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)</td>
</tr>
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* For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is not to be made. See Table 3 for definitions of abbreviations.
<table>
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Table 3: 2010 ACR/EULAR criteria for RA classification. Patients need at least 6 points to be considered as having RA (Taken from [16]).
RA Disease Activity Measures

Once a patient is diagnosed with RA, a measure to determine the activity of RA is necessary to influence treatment decisions. Several RA disease activity measures have been created, as outlined in Table 4, to determine disease activity centered around a rating of patient perceived function, patient pain, patient global assessment, physician global assessment, number of tender joints swollen joints on physical examination, and ESR or CRP levels [18].

Table 4: Outline of the components of several RA disease activity measures according to the clinical signs and symptoms they assess. Taken from [18].

In 2012, the ACR recommended that clinical disease activity index (CDAI), disease activity score with 28 joints (DAS28), patient activity scale (PAS), routine assessment of patient index data (RAPID-3), and simple disease activity index (SDAI), as the five optimal measures for point-of-care RA disease activity measurement [19].
In comparing and contrasting these disease activity measures, DAS28 with ESR or CRP is considered to be a strong measure for clinical practice and research because it includes both patient input and objective clinical findings, but is limited in clinical utility by the requirement for simultaneous laboratory, patient, and clinician measures that are time consuming and may not be able to be efficiently measured in all patients, particularly in typical clinical practice. Since laboratory measures are sometimes only obtained when there is a suspicion for flare, clinical use might bias towards patients with more active disease. The requirement of laboratory measures similarly limits the clinical use of SDAI. RAPID-3 and PAS are the easiest to be administered because they can be conducted, even remotely, by patient surveys, due to only requiring patient function and patient assessment surveys. However, both are limited since they are completely composed of subjective patient measures without clinician or objective input.

The CDAI is an ideal combination of efficient use of clinician time and patient input without the requirement for laboratory measures. As discussed later, other factors, in particular obesity, may falsely elevate ESR and CRP, making CDAI a particularly ideal measure in a population that includes many obese patients. Including patient and physician global scores and a swollen joint count (SJC) and tender joint count (TJC) makes the CDAI an efficient and clinically relevant measure for assessing RA disease activity during patient appointments.

Treatments for RA
Disease activity measures for RA allow clinicians an efficient and quantitative method for determining if treatments are effective by assessing changes in disease activity scores after initiating a treatment. In addition, disease activity measures have provided for an effective method to decide which of the numerous treatment options available are best to use based upon disease activity and severity.

Pharmacologic treatment options for RA span a wide range of drug classes, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs) of which there are two subclasses: non-biologic DMARDs and biologic DMARDs [20, 21]. The ultimate goal of treatment for a RA patient is to “alleviate pain, restore patient quality of life, and ultimately, preserve their independence and ability to perform activities of daily living and vocational, and avocational pursuits” [22].

NSAIDs have been a treatment option for RA over many decades. Their use is to relieve the symptoms of inflammation by inhibiting the enzyme cyclooxygenase important in the creation of prostaglandins which mediate inflammation and in turn which decreases joint swelling, tenderness, and pain [20]. NSAIDs are an inexpensive and widely available oral medication that can treat symptoms from inflammation quickly [23]. Negatively, NSAIDs have potentially serious gastrointestinal, renal, and cardiac side effects especially when used chronically in high doses such as RA patients often would need, and they do not modify the intrinsic disease process of RA.
Corticosteroids, such as prednisone, are fast-acting anti-inflammatory drugs that inhibit a multitude of inflammatory and immune system mediators [20]. Corticosteroids are very effective in quickly controlling an episode of RA flare, but are not preferred for long-term use since they have numerous side effects and also do not appreciably modify the disease process of RA [24]. In particular, corticosteroids have metabolic side effects such as weight gain so their use may indicate both disease activity and contribute to excess weight. Since corticosteroids work are fast-acting and effective for reducing inflammation, they are still commonly used despite the availability of many other options for RA treatment.

The inception of DMARDs revolutionized the treatment of patients with RA by offering well-tolerated medications that could directly target RA pathways and halt the progression of disease with acceptable side effects [25]. The first DMARDs used were non-biologic DMARDs, that nonspecifically target T cells to suppress the immune system and decrease inflammatory processes [26]. Methotrexate is the standard of care for initial treatment of patients with moderate or severe RA. Methotrexate affects a multitude of inflammation pathways and cytokines including reduction of adenosine, dihydrofolate reductase, IL-2, IL-1, and IL-6 [27]. Other non-biologic DMARDs commonly used to treat RA are outlined in Table 5.
Biologic DMARDs revolutionized the treatment of RA by offering drugs that target a specific pathway in the pathogenesis of the inflammatory response related to RA typically using precisely targeted antibodies[7]. A list of biologic DMARDs is shown in table 5. Biologic DMARDs powerfully reduce inflammation and prevent downstream consequences allowing many patients to live without deformities and disability as well as potentially decreasing morbidity and mortality. While the benefits may be powerful, biologic DMARDs can have serious side effects including fatal serious infections and are very expensive. In addition, since biologic DMARDs are antibodies, they cannot be given orally so have to be given by subcutaneous injection or intravenous infusion and may be inconvenient for patients. Also, biologic DMARDs have special storage requirements so may be unavailable to patients with low socioeconomic status or who live in developing countries.

<table>
<thead>
<tr>
<th>Non-Biologic DMARDs</th>
<th>Biologic DMARDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate (Rheumatrex)</td>
<td>Etanercept (Enbrel)</td>
</tr>
<tr>
<td>Sulfasalazine (Azulfidine)</td>
<td>Adalimumab (Humira)</td>
</tr>
<tr>
<td>Hydroxychloroquine (Plaquinil)</td>
<td>Infliximab (Remicade)</td>
</tr>
<tr>
<td>Leflunomide (Arava)</td>
<td>Rituximab (Rituxan)</td>
</tr>
<tr>
<td>Azathioprine (Imuran)</td>
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<td>Anakinra (Kineret)</td>
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<td>Mycophenolic acid (Myfortic)</td>
<td>Tocilizumab (Actemra)</td>
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<tr>
<td>Cyclosporine-A</td>
<td>Certolizumab pegol (Cimzia)</td>
</tr>
<tr>
<td>Gold</td>
<td>Golimumab (Symponi)</td>
</tr>
<tr>
<td>D-Penicillamine</td>
<td>Tofacitinib (Xeljanz)*</td>
</tr>
</tbody>
</table>

**Table 5: Commonly used DMARD medications:** Drug Name (Trade Name) * tofacitinib is a small molecule given orally that inhibits tyrosine kinase, but has targeted effects similar to biologic DMARDs.
Non-Biologic Factors Affecting RA

Although the cause of RA is unknown, there are several factors that have been proven to play a role in disease incidence and ongoing activity. Studies investigating incident RA show that sex plays a significant role, with RA being 3-fold more likely to occur in women [28]. Age also plays a significant role in RA incidence. Although total RA incidence is 41 out of 100,000 people in the US, this rate increases with age and peaks at ages 65-74 where overall incidence rates are 89.4 out of 100,000 people, nearly double the rate of all younger ages [1]. When this incidence is stratified by gender, the peak incidence rates for females are during ages 40-50 while male incidence peaks later in life, at age 70 [29]. This age gap of peak incidence suggests a sex or hormone related role in RA pathogenesis. Environmental factors have also been shown to both increase RA risk and also exacerbate disease activity. Smoking has been shown to greatly increase RA risk and also lead to worse disease outcomes. Smokers with over 25 pack years of smoking have been observed to be over 3 times more likely to develop seropositive RA and more than two-fold likely to develop radiographic erosions [30]. In addition to smoking, socioeconomic status may have a profound effect on RA disease activity. In one study, low socioeconomic status showed to have an odds ratio (OR) of 3.3 ( [95% confidence interval [CI] 1.6, 6.7) for high disease activity when compared to RA patients with high socioeconomic status [31].
Obesity

Obesity, defined by the World Health Organization (WHO) as BMI over 30 kg/m², is a rapidly growing epidemic in the US [32]. Currently, 34.9% of adults age 20 years or older are obese in America [33]. This rampant problem is truly global as BMI has increased by 0.4 kg/m² per decade over the past three decades [34]. Within the US from 2000 to 2010, the prevalence of people with a BMI over 30 kg/m² increased from 19.8% to 27.2% alone [34]. The rapidly expanding waistline of the country has been also taking a toll on healthcare spending. In 2008, obesity related healthcare costs were estimated to be $147 billion, nearly double that of 1998 [35]. Furthermore, obesity has been linked to increasing the disease burden in the population by raising the risk for chronic diseases including but not limited to hypertension, diabetes mellitus, and coronary artery disease in addition to RA [36].

Obesity consists of the over accumulation of white adipose tissue in the body, as an energy storage of triglycerides. White adipose tissue is an essential reservoir of fatty acid storage which is helpful for glucose regulation in times of energy depletion [37]. Adipocytes in white adipose tissue secrete adipokines [38] that are important in inflammatory pathways in the body by the production of IL-6, TNF-α, CRP, ESR, and monocyte chemoattractant protein 1 (Figure 2) [39]. It is hypothesized that adipokines mediate systemic inflammation and have distant organ specific effects, particularly the liver and muscle[40]. This forms a positive feedback loop in obesity that results in perpetual low-grade systemic
inflammation [39]. It is hypothesized, though not proven, that this inflammatory milieu from obesity may also contribute to systemic inflammation in obese patients with RA.

**Obesity and RA**

Although it is accepted that obesity causes an increase in inflammatory pathway mediators, the exact biologic effects of obesity on RA is not fully understood. Several studies have shown associations between obesity and RA indicating that the two diseases likely affect each other. Obesity was associated with increased incidence of RA across men and women (OR 1.24 [95% CI 1.01, 1.53] compared to normal BMI) [41]. This association was even stronger among women in the Nurses’ Health Studies, with obese women under age 55 [Hazard Ratio (HR) 1.65 (95%CI 1.34, 2.05)] having increased risk of later developing RA compared to normal and underweight women [42]. Meta-analysis of 11 studies that compared incidence of RA in obese versus non obese patients showed that obese patients had a relative risk of 1.25 (95%CI 1.07, 1.45) of developing RA compared to normal BMI [43].
Clinically, the association of obesity and RA has been shown through the observation of worse disease activity measures on obese patients as compared to normal weight patients, in several studies. Obesity has been associated with worsened measures of DAS28, modified health assessment questionnaire (MHAQ) (a survey that assessed a patient’s daily function), the clinical visual analog scale (a 0-10 scale of physician's opinion of disease activity (VAS) and patient VAS) compared to normal BMI [44]. A study found that CRP and HAQ were significantly worse for patients that were obese compared to those with
normal BMI [45]. Another study found increasing continuous BMI to be positively correlated with DAS28 \((r=0.34, p=0.001)\) [46]. Furthermore, obese patients with RA have a lower quality of life and less functional capacity, than patients with normal BMI [47]. Overall, these studies show that obesity may be associated with worsened RA disease measures. However, these studies were mostly performed in cross-sectional studies, so it is possible that patients with higher disease activity may be more likely to be obese due to decreased physical activity, medications such as corticosteroids, and a sedentary lifestyle. Additionally, clinically evaluating swollen and tender joints may be more difficult on obese individuals and obese patients typical complain of more tenderness which could be confused with RA disease activity [48]. Longitudinal, prospective studies evaluating the effect of obesity and weight change have not been reported.

In addition to the worsened disease activity measures in obesity, treatments for RA have been shown to be less effective among obese patients. Patients who were overweight and obese had 51% lower odds of being able to achieve low disease activity and 42% lower odds of achieving remission when compared to normal weight patients [49]. These results were again shown in another study where high BMI was independently associated with failure to achieve a DAS28 in the clinical remission category, on initial combination DMARD therapy with prednisone [50]. Anti-TNF medications may also be less effective in the obese population. Obese patients were significantly more likely to
have active disease compared to normal weight patients on Anti-TNF medications (OR 2.63 [95%CI, 1.31, 5.26]) [51].

Although obesity has shown to be detrimental to almost every aspect of RA including diagnosis, treatment, and outcomes, there is a paradox that obese patients have a protective effect on joint destruction in RA. This protective effect has been coined the obesity erosion paradox. BMI has been shown to be significantly inversely correlated with the Sharp-van der-Heijde score (used to assess radiographs for erosions and deformities) [52]. Assessing for erosions on a two-year MRI image follow-up, higher BMI was independently associated with a lower probability of progression of erosions [53]. A meta-analysis further showed the obesity erosion paradox on overall joint destruction: radiographic joint damage was negatively associated with obesity with a standardized mean difference of -0.15 (CI 95% -0.29, -0.02; p=0.03) [54]. The obesity erosion paradox suggests that obese patients with RA may have a more modifiable disease phenotype compared to patients with normal BMI. Some adipokines, in particular adiponectin, might paradoxically have anti-inflammatory effects in certain tissues, perhaps in the synovium though this is still controversial.

In total, research suggests that obesity negatively affects RA with the exception of the obesity erosion paradox. An important research question now is whether modifying weight also modifies many of the negative impacts of obesity on RA. Research on weight change in RA has been scarce, as most studies on obesity and RA evaluate obesity categories, comparing obesity and overweight
to normal BMI. One study conducted by Sparks et al, followed RA patients before and after bariatric surgery for weight loss [55]. In this study patients lost a mean of 41 kg twelve months after bariatric surgery. This significant weight loss correlated to decreased RA disease activity measures, less medication usage, and decreased serum inflammatory markers [55]. However, there was no control group and all patients lost weight through surgical intervention. Another prospective cohort study investigated typical weight gain and RA disease activity and found no significant association, but did not evaluate weight loss [44].

Since extreme weight loss due to surgical intervention showed significant improvements in RA disease activity, studies of typical weight change and RA disease activity are now necessary. We therefore aimed to investigate longitudinal weight change and its effects on ΔCDAI in RA patients.
OBJECTIVES

Studies have associated obesity with increased systemic markers of inflammation. Studies showed that obesity and overweight are associated with increased disease activity measures, higher medication use, and a lower probability of being able to reach remission or low disease activity states compared to normal BMI. The majority of these studies have found these associations in cross-sectional designs. Major weight change through surgical intervention has been shown to have a significant impact on RA disease activity and disease outcomes. There exists a gap in our understanding of whether typical weight loss may be a modifiable factor to improve RA disease activity.

This thesis seeks to describe the impact that typical weight change has on RA disease activity, as measured by CDAI. In addition, this paper seeks to describe if weight loss, defined by a significant decrease in BMI, will be associated with decreased CDAI measures. We hypothesize that a change in BMI will be associated with changes in CDAI measures. Specifically, we anticipate to observe that an increase in BMI will be associated with an increase in CDAI and a decrease in BMI will be associated with a decrease in CDAI.
METHODS

Study Sample and Data Source

We conducted a retrospective cohort study of RA patients who had two or more CDAI measures and corresponding BMI measures on the same dates using data from the electronic medical record (EMR). Patients with RA were identified by querying for patients with at least one International Classification of Diseases, Ninth Revision (ICD-9), a coding system used for billing and reporting purposes, for RA (714.0) in the Partners Research Patient Database Repository prior to 7/1/2014. We then identified patients that had at least two CDAI measures in the EMR. Medical record review determined RA according to either the 1987 ACR or 2010 ACR/EULAR criteria for RA to be included in this study. Patients that did not have at least two separate BMI measures within one week of each CDAI measure were excluded. Figure 3 shows a flow diagram illustrating the sample for analysis, all 178 subjects identified were seen at Brigham and Women’s Hospital for their rheumatology care.

Data Collection

After identifying patients that qualified for the study, detailed medical record review was performed. The visit dates for medical record review was conducted as outlined in Figure 4. Each CDAI measure with corresponding BMI became the baseline visit date (T₁), and then each sequential CDAI measure with a BMI measure was an additional visit. Each subject had at least two visit dates. At each visit date, sociodemographic, lifestyle, medication usage,
questionnaire data, RA characteristics, laboratory values, and comorbidities were collected.

Figure 3: Flow diagram illustrating the analyzed study sample. ACR = American College of Rheumatology, BMI = body mass index, BWH = Brigham and Women’s Hospital, CDAI = Clinical Disease Activity Index, EULAR = European League Against Rheumatism MGH = Massachusetts General Hospital, RA = rheumatoid arthritis.
Figure 4: Schematic of data collection. \( T_1 \) indicates the baseline visit date (first CDAI recorded with corresponding BMI). Each subsequent \( T_n \) are subsequent time points where CDAI and BMI were measured. Vertical lines coincide to time points where medical record review was performed to collect data on sociodemographics, lifestyles, medication usage, questionnaires, RA characteristics, laboratory values, and comorbidities.

**Primary Exposure**

BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m\(^2\)). This was calculated from measured weights of subjects within one week of CDAI assessment (most often on the day of CDAI measurement). Since our study was over three years, we assumed that height would remain stable. The mode of the height was therefore used for each subject. Height was recorded in inches, and weight in pounds. We used the WHO classification of BMI, categories for underweight (<18.5), normal weight (18.5 to <25.0 kg/m\(^2\),
overweight (25.0 to <30 kg/m$^2$), obese I (30.0 to <35 kg/m$^2$), obese II (35.0 to <40 kg/m$^2$), and obese III (BMI ≥40.0 kg/m$^2$), to categorize BMI values at each visit. Additionally, subjects were categorized as being obese (BMI ≥30 kg/m$^2$) or not obese (BMI <30 kg/m$^2$).

**Outcome Measure**

The outcome measure for this study was CDAI. CDAI is an ACR recommended RA disease activity measure that quantifies disease activity on a scale of 0-76 with validated cutoffs of ≤2.8 for remission, >2.8 to ≤10 for low disease activity, >10 to ≤22 for moderate disease activity, and >22 for high disease activity [19]. This measure was made available by an electronic tool for use in the EMR at BWH. This tool was available starting in 2012 for a quality improvement program to document disease activity for patients with at BWH. As part of this initiative, a research assistant at BWH was available to facilitate collection of patient-derived measures in order to limit the burden on the treating rheumatologist who performed clinically derived measures of global assessment and joint counts.

CDAI is calculated by adding the swollen joint count (SJC), tender joint count (TJC), patient global assessment, and physician global assessment. SJC and TJC were derived from BWH rheumatologists palpating either 28 or 68 individual joints that are shown in figure 5 making the official test either a CDAI (28) or CDAI (68). Patient global assessment and physician global assessment
are both subjective assessments of disease activity, rated on a scale of 0-10 with 0 being none and 10 being the worst.

**Figure 5: Homunculus of 68 joints assessed in CDAI measures.** Image of joints assessed in the CDAI for being swollen or tender. CDAI (28) includes all joints labeled in blue. CDAI (68 includes all joints labelled in blue and red.

In addition to the total CDAI score being recorded, we recorded the SJC and TJC counts. If a 68 joint count was taken by the physician this was recorded and also converted to a 28 joint count, so that every subject had a SJC and TJC count on the 28 joint scale. Additionally, patient and physician global assessments were collected. Lastly, for every CDAI measure, the wrists, 1st-5th metacarpophalangeal joints (MCP), 2nd-5th proximal Interphalangeal joints (PIP), and the interphalangeal joint of the thumb (IP) for the right and left hands
were recorded individually indicating if they were normal, swollen, tender or both tender and swollen.

**Covariates**

In addition to the exposure and outcome data, we also collected covariate data at each visit, including sociodemographics, lifestyles, medication usage, questionnaire data, RA characteristics, laboratory values, and comorbidities. Most of the sociodemographic data were collected only at the baseline visit date, since these were unlikely to change during follow-up, with the exception of age, employment status, and health insurance which were collected at each time point. Age was collected as a continuous variable in years. Employment status was categorized as working, unemployed, retired, disabled, or student. Health Insurance was categorized as having private insurance, Medicare, Medicaid, or combinations. Sex was collected as a binary variable of being male or female. Education was categorized as less than high school (12th grade or lower), high school graduate (or equivalent), some college, college graduate, graduate degree, or unknown. Race was categorized as White, Black, Asian, or American Indian/Alaskan Native. Ethnicity was dichotomized as Hispanic/Latino or not Hispanic/Latino.

We collected lifestyle information on smoking status for subjects at each visit. Smoking was categorized as being a current, past, or never smoker at each visit. This was further dichotomized as ever or never being a smoker at each visit.
Medication usage was collected at each visit. Biologic and non-biologic DMARDs were recorded based upon the specific DMARD that was being taken at the time of CDAI (listed in Table 5). Additionally, the methotrexate dosage (in mg/week) was recorded. Dosage and the specific type of corticosteroid was also recorded at each visit. Present medication usage at each visit was recorded for the following drug classes: NSAIDs, insulin, oral hypoglycemics (metformin, glyburide, and glipizide), statins, and opioids.

Questionnaire data specific to RA were recorded. The questionnaire data, which was part of the quality improvement project at BWH to increase validated measures of disease activity, included four components. While all patients in this study had CDAI measured, patients were not obligated to answer these additional questions, so these were only available in a subset. The Modified Health Assessment Questionnaire (MHAQ) score, which ranges from 0-2 with 0 being fully functional and 2 being unable to do daily activities, [56]. The subject’s opinion of their disease activity over the past 6 months on a scale of 0-10, 10 being the worst. The same question, but for their activity on the day of the appointment, and a 0-10 scale rating of their current level of pain. A question evaluating the experience of morning stiffness by the subject with possible responses of no morning stiffness, >30 minutes of stiffness, 1-2 hours of stiffness, 3-4 hours, and all day stiffness.

RA disease specific characteristics were also recorded at each time point, as outlined in Table 7. The RA diagnosis date was recorded to calculate the RA
disease duration from diagnosis to each visit. The presence of bone erosions
was recorded based upon radiology reports from board certified radiologists. The
presence of deformities was recorded from treating physician’s medical record
notes. The presence of interstitial lung disease (ILD), an extra-articular RA
disease manifestation, was recorded [57]. RA-related autoantibodies were
recorded only once, as these tests are unlikely to change or be rechecked over
time. The specific laboratory values for RF and ACPA were recorded in units/ml.
These were dichotomized as positive or negative for RF and ACPA according to
clinically accepted cutoffs. This was further categorized as being seropositive
(positive for RF and/or CCP) or seronegative (negative for both RF and CCP). If
a patient was referred to as being seropositive in medical record notes, this was
recorded as being seropositive even if laboratory values were not available since
these tests might have been performed at other institutions.

In addition to RA-specific laboratory values, other laboratory values were
recorded at each visit. These included CRP, ESR, white blood cell counts,
hemoglobin, hematocrit, platelets, hemoglobin A1c, creatinine, albumin, alkaline
phosphates, alanine aminotransferase, aspartate aminotransferase, total
bilirubin, low density lipoprotein, high density lipoprotein, triglycerides, and total
cholesterol. These measures were recorded as clinically available. Since these
were not checked on every patient at every visit, many patients had missing
laboratory values.
The presence of comorbidities was recorded at every visit. The comorbidities recorded included osteoarthritis (further categorized small joint, large joint, or spine), fibromyalgia, dyslipidemia, diabetes, coronary artery disease, chronic obstructive pulmonary disorder, depression, asthma, osteoporosis, hypothyroidism, hyperthyroidism, hypertension, stroke, cancer, chronic heart failure, peripheral vascular disease, chronic liver disease, gastrointestinal reflux disease (GERD) and chronic kidney disease.

**Statistical Analysis**

We calculated descriptive statistics including frequencies, mean, median, range, interquartile range, and standard deviation among the entire study sample and also stratified by exposure status. We performed univariate tests to investigate whether sex, age, RA duration, smoking status, serologic status, and steroid usage were associated with the exposure and outcome, using t-tests for continuous normally distributed variables, Wilcoxon rank-sum tests for continuous non-normally distributed variables, chi-square tests for categorical variables, and Fisher’s exact tests for categorical variables with small cell sizes. These specific confounders were selected due to their previously defined significance of affecting RA disease activity in clinical studies [58-63].

We used linear regression on the entire study population to assess whether $\Delta BMI_{min-max}$ is associated with change in CDAI measures, and considered. Adjusted linear regression was further performed, adjusting for the above listed confounders, to test for the effects on the results. $\Delta BMI_{min-max}$ was
determined by evaluating the clinical study visits with the maximum BMI observed and minimum BMI for each study subject. By doing this, we were able to standardize each subject to having only two study visits. In addition, we were able to quantify BMI change as positive or negative by subtracting the first chronological BMI taken by the second chronological BMI calculating a maximum $\Delta$BMI for every patient. If the value was negative, it indicated that weight was lost between the two extreme weight visits, and if the value was positive weight was gained between the two extreme weight visits.

The subject population was stratified into three groups, BMI loss, BMI stable, and BMI gain, unadjusted linear regression was used to test for a significance between $\Delta$BMI$_{\text{min-max}}$ and change in CDAI within each of these three groups. BMI loss was defined as $\Delta$BMI $<-1$ kg/m$^2$, BMI stable was categorized as $\Delta$BMI between -1 and 1 kg/m$^2$, and BMI gain was categorized as $\Delta$BMI $>1$ kg/m$^2$. These categories and definitions were chosen due to them previously being defined as significant measures for BMI change by Baker et al [64]. Logistic regression was performed to evaluate whether BMI categories were associated with low or remission by CDAI, defined as a CDAI <10. From this odds ratios (OR) were calculated, as well as 95% CI.

The data was analyzed using SAS 9.4® Software. A two-sided p value of <0.05 was considered statistically significant in all analyses.
RESULTS

Descriptive Statistics

We identified 178 RA subjects that met our inclusion criteria of having a minimum of two clinical visits where CDAI score and BMI was measured in the EMR. A total of 854 clinical visits were recorded from this sample, with a median of 5 clinical visits per subject, and a range of 2 to 11 clinical visits. Study visits included in these analyses occurred between 3/26/2012 and 5/29/2015. The mean age of at baseline study 60.2 years (standard deviation [SD] 13.5), 84.2% of subjects were female, and 84.2% were white, 55.0% had ever smoked, 50.6% had received a college or greater education, 45.5% were retired and 49.4% were on private medical insurance plan. The most common comorbidities were osteoarthritis 67.4%, hypertension 51.7%, and GERD 29.2% (Table 6).

At the initial CDAI measure, the mean BMI was 28.4 kg/m² (SD 6.25), with 33.7% of subjects classified as underweight or normal, 34.3% of subjects being overweight and 32.0% of subjects being classified as obese. The mean RA duration was 11.9 years (SD 9.5) with 77.5% being seropositive, 53.4% having evidence of radiographic erosions and 14.6% having deformities from RA. The mean CDAI score was 13.6 (SD 11.1) with 6.7% of subjects in remission, 44.4% with low disease activity, 29.2% with moderate activity and 19.6% at high disease activity (Table 7).
<table>
<thead>
<tr>
<th>Variable</th>
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<th>Variable</th>
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<td>Self Paid</td>
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Table 6: Subject sociodemographics, lifestyle factors, BMI, and comorbidities at baseline. The mean and standard deviation are defined for continuous variables, and frequency and percent are defined for dichotomous variables. GERD = gastroesophageal reflux disease, CAD = coronary artery disease, COPD = chronic obstructive respiratory disease. BMI obesity was classified as an BMI of >30 kg/m². BMI categories were classified by WHO classification of BMI, categories for underweight (<18.5), normal weight (18.5 to <25.0 kg/m²), overweight (25.0 to <30 kg/m²), obese I (30.0 to <35 kg/m²), obese II (35.0 to <40 kg/m²), and obese III (BMI ≥40.0 kg/m²).
NSAIDs were used by 52.8% of patients, 17.4% used opioids, 31.4% were on steroids, 48.9% were on methotrexate, 14.6% were on other non-biologic DMARDs, 59.6% were on biologic DMARDs, and 87.1% were taking any DMARDs. Questionnaire data on the experience of morning stiffness was available for 97 patients at baseline with 18.5% reporting no morning stiffness, 41.2% reporting morning stiffness of 30 minutes or less, 25.7% experiencing morning stiffness of 1-2 hours, 5.2% 3-4 hours and 9.3% having all day stiffness. MHAQ questionnaire data was available for 133 subjects at baseline with a mean score of 0.3 (SD 0.44) (Table 7).
Table 7: RA disease characteristics, disease activity measures and medication usage. The mean and standard deviation are defined for continuous variables, and frequency and percent are defined for dichotomous variables. CDAI scores were quantified by using 28 joint count CDAI assessment, and the score range was from 0-76. MHAQ was quantified on a 0-2 scale with 0 meaning no impairment on daily function and 2 being major impairment of daily function. Questionnaire data was quantified on a 0-10 scale with 10 being maximum activity or pain. and 0 being no activity or pain. ACPA = Anti Anti cyclic citrullinated protein, CDAI= clinical disease activity index, CRP= C-reactive protein, DMARDs= disease-modifying antirheumatic drug, ESR= erythrocyte sedimentation rate, ILD= Interstitial lung disease, RA=rheumatoid arthritis and RF= rheumatoid factor.
Associations of ΔBMI with ΔCDAI

The primary hypothesis was to observe the effect that ΔBMI would have on ΔCDAI. Unadjusted linear regression was performed on all 178 subjects to analyze the overall trend within the sample population. For every 1 kg/m² increase in BMI, CDAI increased by 0.49, but these results were not statistically significant (p=0.155, 95%CI -0.176, 1.097). No significant associations were found after adjusting for confounders including adjusting for sex, age, disease duration, smoking status, serologic status, and steroid usage. The change in BMI was observed to be non-significant as well with a β=0.493 (p=0.1264, 95%CI 0.14, 1.12) (Table 8).

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>p value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔBMI</td>
<td>0.493</td>
<td>0.126</td>
<td>-0.141 - 1.127</td>
</tr>
<tr>
<td>Female</td>
<td>-2.704</td>
<td>0.161</td>
<td>-6.495 - 1.087</td>
</tr>
<tr>
<td>Age</td>
<td>-0.083</td>
<td>0.139</td>
<td>-0.193 - 0.027</td>
</tr>
<tr>
<td>RA duration</td>
<td>0.029</td>
<td>0.715</td>
<td>-0.126 - 0.183</td>
</tr>
<tr>
<td>Smoking status</td>
<td>1.526</td>
<td>0.269</td>
<td>-1.188 - 4.241</td>
</tr>
<tr>
<td>Seropositivity</td>
<td>2.424</td>
<td>0.147</td>
<td>-0.864 - 5.711</td>
</tr>
<tr>
<td>Steroid Usage</td>
<td>-1.507</td>
<td>0.315</td>
<td>-4.458 - 1.444</td>
</tr>
</tbody>
</table>

**Table 8: Adjusted linear regression for ΔCDAI.** All covariate data was based upon the baseline visit for each subject. Smoking status was quantified as a binary variable of ever being a smoke or never being a smoke. Steroid usage was quantified as taking any dosage of steroids at the baseline visit.

To further investigate the associations between ΔBMI and ΔCDAI, subjects were stratified into three groups, BMI gain, stable BMI, and BMI loss. Unadjusted linear regression was performed on these three models for ΔCDAI (Table 9).
<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>β</th>
<th>p value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI loss</td>
<td>58</td>
<td>-2.606</td>
<td>0.028</td>
<td>-4.913 to -0.298</td>
</tr>
<tr>
<td>BMI stable</td>
<td>65</td>
<td>1.947</td>
<td>0.171</td>
<td>-0.863 to 4.756</td>
</tr>
<tr>
<td>BMI gain</td>
<td>55</td>
<td>-0.053</td>
<td>0.956</td>
<td>-1.966 to 1.860</td>
</tr>
</tbody>
</table>

Table 9: Unadjusted Linear Regression for ΔCDAI, Stratified by BMI gain, stable, loss. BMI gain=a positive ΔBMI >1, BMI stable= absolute ΔBMI <1, BMI loss=a negative ΔBMI >1. BMI=body mass index.

A significant association was found in the BMI loss group with a β=-2.61 (p=0.028, CI -4.91, -0.298). A scatter plot for this regression can be seen in Figure 6. To test the strength of the association found in the BMI loss group, adjusted linear regression was performed on this group adjusting for sex, age, disease duration, smoking status, serologic status, and steroid usage. The association remained significant with a β=-2.499 (p=0.044, CI -4.94, -0.061).

Amongst those who lost >1 kg/m², for every kg/m² lost CDAI decreased by -2.499. In the BMI stable and BMI gain groups, no significant association was found with β=1.945 (p=0.17, CI -0.863, 4.75) and β=-0.053 (p=0.956, CI -1.97, 1.86), respectively.
Figure 6: Scatter plot of the unadjusted linear regression for BMI loss group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>p value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔBMI</td>
<td>-2.499</td>
<td>0.044</td>
<td>-4.937 to -0.061</td>
</tr>
<tr>
<td>Female</td>
<td>-6.846</td>
<td>0.064</td>
<td>-14.091 to 0.399</td>
</tr>
<tr>
<td>Age</td>
<td>-0.087</td>
<td>0.418</td>
<td>-0.302 to 0.128</td>
</tr>
<tr>
<td>RA duration</td>
<td>-0.118</td>
<td>0.550</td>
<td>-0.511 to 0.275</td>
</tr>
<tr>
<td>Ever smoking</td>
<td>3.465</td>
<td>0.236</td>
<td>-2.341 to 9.272</td>
</tr>
<tr>
<td>Seropositivity</td>
<td>1.322</td>
<td>0.713</td>
<td>-5.858 to 8.502</td>
</tr>
<tr>
<td>Steroid use</td>
<td>0.986</td>
<td>0.769</td>
<td>-5.719 to 7.690</td>
</tr>
</tbody>
</table>

Table 10: Adjusted linear regression for ΔCDAI in the BMI loss group. All covariate data was based upon the baseline visit for each subject. Smoking status was quantified as a binary variable of ever being a smoke or never being a smoke. Steroid usage was quantified as taking any dosage of steroids at the baseline visit. BMI=body mass index.
Associations of ΔBMI with Low/Remission Disease Activity

As a secondary analysis, we tested to see if BMI change was associated with a dichotomous variable of low/remission RA disease activity, as defined by a CDAI score <10 at the later clinical visit used in the BMImin-max analysis. Unadjusted logistic regression was performed on all study subjects for ΔCDAI. The results were not statistically significant with an OR 0.990 (95% CI 0.855, 1.146).

The subjects were further stratified into the BMI gain, stable, and loss groups as defined above for the linear regression model. Unadjusted logistic regression was performed on all three stratified groups to evaluate if BMI change within these groups was associated with low/remission RA disease activity. The BMI loss group were less likely to achieve low or remission RA disease activity with an OR 0.882 (95%CI 0.363, 2.139), but these results were not statistically significant. No significant associations were found in the BMI gain or stable groups (Table 10).

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>OR</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI Loss</td>
<td>58</td>
<td>0.882</td>
<td>0.363</td>
</tr>
<tr>
<td>BMI Stable</td>
<td>65</td>
<td>0.995</td>
<td>0.658</td>
</tr>
<tr>
<td>BMI Gain</td>
<td>55</td>
<td>1.452</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Table 11: Unadjusted logistic regression for ΔCDAI as a predictor for low or remission RA disease activity. RA disease activity of low or remission was defined as a CDAI <10 at the second clinical visit used in the BMI min-max analysis. BMI=body mass index, OR=odds ratio.
DISCUSSION

We showed that in patients with RA that lost weight were significantly associated with decreased RA disease activity as measured by CDAI, in the routine clinical setting. For each BMI point lost above 1 kg/m\(^2\), CDAI decreased by 2.499 per kg/m\(^2\) independent of sociodemographic and RA characteristics. These results build on prior literature that showed that obesity is associated with worsened RA disease activity measures in cross-sectional designs. Our results are consistent with a longitudinal study that showed significant improvements in RA disease activity and RA disease outcomes when weight loss was achieved through surgical interventions. This is the first longitudinal study to demonstrate a significant relationship between weight loss and disease activity in the typical clinical setting.

Summary of Results

Descriptive statistics recorded at baseline allowed us to make several generalizations about the study population utilized in this paper. The population was primarily comprised of late-middle aged, white, females, with the majority receiving higher education and having medical insurance, which is typical of RA patients seen at BWH. With regards to RA, the subjects had primarily longstanding RA, were seropositive, were taking a DMARD, many had radiographic erosions, and had disease activity quantified by CDAI mostly in the low to moderate range. All of these sociodemographic and RA disease
characteristics at baseline were similar to the baseline characteristics seen in a study that measured CDAI from Consortium of Rheumatology Researchers of North America (CORRONA), a prospective observational United States research registry of patients with RA [65]. This indicates that our study population may be generalizable to other RA populations.

By stratifying into groups of BMI gain, stable, and loss, we were able to observe that a BMI loss of greater than 1kg/m² was significantly associated with a decrease in CDAI measures, for both unadjusted and adjusted linear regression models. No significant association was found within the BMI stable and gain groups. The observation of no significant association in the BMI gain group is consistent with a previous study [44]. This indicates that weight loss may be a more important factor for affecting disease activity compared to weight gain. This finding shows promise that weight loss may be a potential intervention for RA patients. However, we were unable to record whether weight loss was intentional, we did not have data on diet and physical activity. We were able to record comorbidities at the time of study visits but it is possible that undiagnosed chronic diseases such as cancer might have influenced weight loss. We did have rich data available on other potential confounders, such as age, sex, education, insurance, RA duration, serostatus, bone erosions, smoking, steroid usage, and DMARD usage. Our results remained significant after adjustment for these variables, arguing that the effect of residual confounding from unmeasured factors was minimal.
Lastly, in analyzing changes in BMI as a predictor for low or remission RA disease activity, no significant associations were found using logistic regression. Logistic regression models were repeated on the study sample stratified by BMI gain, stable, and loss categories and no significant predictive association was found for any of the groups. From this, our study cannot say whether or not weight change can predict changes to clinically meaningful disease activity categories. One possibility is that our study was underpowered to find a true association in the logistic regression analysis. Prior studies have shown that overweight and obese had 51% lower odds of being able to achieve low disease activity and 42% lower odds of achieving remission when given comparable treatments to normal weight patients [49]. A larger study would be necessary to see if weight change can also have an impact on disease activity categories.

**Strengths and Limitations**

The major strength of the study sample analyzed in this paper was the availability of multiple CDAI measures in the routine clinical setting. Specifically, finding a study sample of this size retrospectively with a minimum of two CDAI measures with correlating BMI measures was a significant task. RA disease activity measures in general and specifically CDAI are typically used to quantify RA disease activity for research studies, and are not routinely collected and recorded for clinical visits. Rather, RA disease activity is typically described qualitatively. When CDAI is recorded for typical clinical use it is typically used for patients switching medications to quantify the effectiveness of the new
medication so it is possible that CDAI clinical visits occurred when patients had active disease. However, we were also able to quantify medications changes in this study. Another factor enabling this study was the effort made by BWH to increase the use of clinical disease activity measures recorded in EMR for RA patients. In this effort, a research assistant was provided to the rheumatology physicians to assist in collecting and recording this data. Therefore, the study sample may have occurred randomly since patients often agreed to have CDAI performed in the waiting room prior to evaluation by the rheumatologist. In future studies, we will be able to adjust for medication changes.

Additionally, it is possible that the study sample may not be generalizable to the general population of patients with RA. Specifically, this sample was collected at BWH, a single center private tertiary care medical institution, and the majority patients in this study were educated and almost all had health insurance and were older, and mostly white. With regards to RA, the subjects had longstanding RA and most had elevated disease activity. Many had seropositive RA with bone erosions and deformities. Our study therefore requires replication in larger studies in diverse patient populations.

The significant association between ΔBMI and ΔCDAI in the BMI loss group may have important clinical implications. For patients with RA, changing their lifestyle to lose weight could provide relief in RA disease activity. Physicians have the potential to add weight loss as an intervention they promote to patients for RA disease activity rather than the other known benefits of reducing weight.
However, we did not find a significant association between weight loss and RA remission/low disease activity, so it is not clear whether our results are clinically meaningful. Further studies in our dataset will evaluate absolute weight loss, weight loss trajectories, and will incorporate repeated measures to further explore this relationship.

All of the other statistical tests performed found results that were not statistically significant. These studies may have been underpowered to detect a true association, but it is also possible that our significant finding was biased, confounded, or due to multiple comparisons. However, we pre-specified this analysis based on prior literature and had rich covariates available for adjustment in multivariable analyses. It is possible that CDAI visits may have systematically occurred in patients with higher disease activity, however a research assistant approached patients randomly and disease activity in our sample was similar to other RA cohorts. A larger study is necessary to replicate the significant relationships that we report and to investigate other outcomes related to weight loss and disease activity.

Length of follow-up was another limitation of this study. All of the clinical visits recorded in this study were taken over a three-year period, and the mean follow-up on each individual subject was 21.6 months. This left a relatively limited window of time that significant weight change could be observed. A prospective study that follows subjects over a longer time period would be able to control for periodic changes of weight by showing longstanding maintained weight change.
Additionally, BMI may not accurately reflect individual's body composition and other measures such as waist/hip ratio, body shape, and adiposity were unavailable. In addition, measured of physical activity, diet, and intention to lose weight were unavailable. Future prospective studies with longer follow-up that include these measures would strengthen the association between weight loss and improved RA disease activity.

**Future Studies**

Overall, the significant results found in this study are promising, but further analysis of the dataset used for this thesis and future studies analyzing the association of weight change and RA disease activity measures are necessary to completely understand this relationship.

Currently, the data collected for this thesis are being further analyzed so that the relationship between changes in BMI and CDAI can be better understood. Time of follow-up between visits is being standardized. By doing this, we will be able to better understand if the rate of weight loss is affecting the results. Current research indicates that rapid weight loss is associated with worse RA outcomes, and in general with serious medical issues [64]. Therefore, our further analysis plans to account for these factors. Additionally, medication usage and changes in medication regimens are being analyzed for the creation of propensity scores to control for medication usage being a major factor for disease activity changes. With further analysis, and by controlling for time and medication changes, other significant relationships between weight change and
disease activity may be found. A relationship between specific DMARDs, steroids, dosage of steroids, dosage of methotrexate can be observed in their relation to disease activity and weight change. In addition, we will use advanced statistical methods accounting for repeated measures to fully utilize the strength of the data collected. We will also classify patients according to weight loss and CDAI trajectories to understand the time-varying course of both measures.

Beyond this study, it will be essential to conduct similar research on larger samples powered to investigate the relationship between BMI exposures and RA disease activity outcomes. An ideal candidate for this future study is the Brigham Rheumatoid Arthritis Sequential Study (BRASS). BRASS is a prospective observational single-center cohort of over 1,400 RA patients at BWH. These patients undergo yearly research study visits where detailed laboratory measures and disease activity measures are taken [66]. Rich phenotypic data on functional status, physical activity, medications, and behaviors are routinely collected. In addition, subjects answer questionnaires every six months to provide interim data. Follow-up up to 13 years is available in BRASS. This cohort therefore has all these measures readily available and would allow for a similar analysis as done in this paper to be conducted on a larger sample albeit with measures taken in the research setting, instead of in the real world clinical setting as in this analysis.

If the results found in this paper can be replicated, it will be necessary to initiate new observational and interventional studies. Specifically, prospective
studies of larger patient populations will lead towards having more power to
detect true associations and more refined, prospective measures of
anthropometrics, metabolic factors, diet, and physical activity. Analyzing the
change in body fat composition would be crucial to furthering the understanding
of how specific changes in body composition affect RA disease activity
measures. These studies would have physiologic implications that different body
tissues are having on RA disease activity, and could ultimately lead to weight
loss becoming a clinical intervention for RA patients.

Currently at BWH, clinical researchers are preparing for an intervention
based clinical trial on weight loss and RA disease activity. By conducting a
randomized controlled trial that observes weight change and RA disease activity
unmeasured confounding can be adequately addressed and translational studies
measuring changes in systemic inflammation and adipokines can also be
performed.

**Conclusions**

We observed that weight loss occurring in the typical clinical setting was
associated with improved RA disease activity. These results may have important
implications for patients, clinicians, and researchers. Further studies analyzing
this relationship are necessary to replicate these results. In the future, weight
loss intervention studies are necessary to determine the relationship between
weight loss and RA disease activity.
LIST OF JOURNAL ABBREVIATIONS

Acta Pol Pharm ........................................... Acta Poloniae Pharmaceutica
Am J Epidemiol ............................................. American Journal of Epidemiology
Am J Med ..................................................... American Journal of Medicine
Ann Rheum Dis ............................................. Annals of the Rheumatic Diseases
Arthritis Care Res ........................................... Arthritis Care & Research
Arthritis Res Ther .......................................... Arthritis Research and Therapy
Arthritis Rheum ............................................. Arthritis & Rheumatism
Arthritis Rheumatol ......................................... Arthritis & Rheumatology
Biochem J ........................................................ Biochemical Journal
Br J Ophthalmol .............................................. British Journal of Ophthalmology
Br J Rheumatol ............................................... British Journal of Rheumatology
Clin Rheumatol ............................................... Clinical Rheumatology
Exper Opin Investig Drugs ......................... Expert Opinion on Investigational Drugs
Health Aff ..................................................... Health Affairs
Health Qual Life Outcomes ................................ Health and Quality Life Outcomes
J Am Diet Assoc .............................................. Journal of the American Dietetic Association
J Pain Res ..................................................... Journal of Pain Research
J Rheumatol ..................................................... Journal of Rheumatology
JAMA ......................................................... Journal of the American Medical Association
Mayo Clinic Proc .............................................. Mayo Clinic Proceedings
Mediators Inflamm ........................................... Mediators of Inflammation
Nat Clin Pract Rheumatol ........................Nature Clinical Practice Rheumatology
Rheumatol Int .............................................................. Rheumatology International
Scand J Rheumatol ....................................................... Scandinavian Journal of Rheumatology
Ther Adv Musculoskelet Dis Therapeutic Advances in Musculoskeletal Disease
West J Med .............................................................. Western Journal of Medicine
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56. Maska, L., J. Anderson, and K. Michaud, *Measures of functional status and quality of life in rheumatoid arthritis: Health Assessment Questionnaire Disability Index (HAQ), Modified Health Assessment Questionnaire (MHAQ), Multidimensional Health Assessment Questionnaire (MDHAQ), Health Assessment Questionnaire II (HAQ-II), Improved Health Assessment Questionnaire (Improved HAQ), and Rheumatoid Arthritis Quality of Life (RAQoL)*. Arthritis Care Res (Hoboken), 2011. 63 Suppl 11: p. S4-13.


CURRICULUM VITAE

David Kreps
• phone: 908-456-2352 • email: dkreps@bu.edu • Year of birth 1992

EDUCATION

Boston University, Boston, MA
Master of Science, Medical Sciences, May 2016 (Anticipated)

Brandeis University Waltham, MA
Bachelor of Science, Health: Science, Society and Policy, May 2014
Bachelor of Arts, Biology, May 2014

HEALTH-RELATED EXPERIENCE

Obesity, Weight Change and Disease Activity Measures in Patients with Rheumatoid Arthritis Brigham and Women’s Hospital, Boston, MA
Research Trainee, Sept. 2015 – present

• This study aims to analyze the relationship between typical weight change and rheumatoid arthritis disease activity measures.

• Conducted detailed medical record reviews for all rheumatoid arthritis patients that met the study inclusion criteria.

• Organized and led study update meetings with other physicians and researchers working on this project.

• Currently using this study for the completion of my thesis requirement for my MS degree, and working on further analyses that will be used for a publishable scientific article.

PRE-RA Family Study, Brigham and Women’s Hospital, Boston MA
Research Trainee, Jan. 2016 – present

• The PRE-RA Family Study is a randomized controlled trial that is evaluating the effect of RA educational programs on an individual’s willingness to change behaviors, within a population of unaffected first-degree relatives of patients with rheumatoid arthritis.
- Conducted detailed medical record review for all of the rheumatoid arthritis affected relatives of study subjects.

- Conducted literature review to analyze the generalizability of the PRE-RA Family Study to other studies of RA relatives.

- Participated in weekly research meeting pertaining to recruitment, follow-up, data management, and analysis.

**Partners Biobank**, Brigham and Women’s Hospital, Boston, MA

- Partners Biobank is the largest biorepository in New England.

- Consented patients to donate DNA samples in 12 different outpatient clinics.

- Participated in weekly research meeting to improve recruitment strategies.

**Boston University Emergency Medical Services**, Boston University, Boston, MA
*Emergency Medical Technician, Field Training Officer*, Sept. 2014 – present
*Lead Instructor*, Feb. 2015 – present

- Worked as an emergency medical responder at Boston University facilities during daily activities and special events by providing medical care according to national and state protocols.

- Trained newly hired EMS personnel for daily operations as a BUEMT. Complete training summary reports for these new employees that are used for clearance to work unsupervised.

- Instructor classes of people taking classes emergency medical services classes at Boston University, including First Aid, CPR, and first responder. In addition, also instruct lab based skill sessions for the emergency medical responder basic course.
Overlook Hospital Internship Program, Overlook Hospital, Summit, NJ  
*Intern*, Jun. 2011

- Selected as one of 12 students from over 80 applicants to shadow various healthcare professionals.

- Scrubbed for various surgeries, conversed with patients in the psychiatry ward, experienced private practice.

Delirium Prevention Program, Overlook Hospital Summit NJ  
*Volunteer*, Jul. – Aug. 2010

- Conversed with patients over the age of 65 in the hospital in an effort to prevent delirium due to hospitalization.

WORK EXPERIENCE

**Brandeis University Admissions** Brandeis University, Waltham, MA  
*Secretarial Aide*, Sept. 2010 – May 2014

- Maintained database of all application materials.

- Prepared promotional packets to be distributed at college fairs and high school visits.

**Brandeis Escort & Safety Service**, Brandeis University, Waltham MA  
*Employee*, Sept. 2012 – May 2014

- Worked during events to maintain safety and help direct visitors of University to their destination.

- Drove University Vans for student’s daily usage and campus events.

**Atlantic and Pacific Tea Company**, Fanwood, NJ  
*Cashier*, Jul. 2008 – Aug. 2010

- Managed cashiers on duty and ensured smooth operation of all purchases in store.
• Prepared daily reports on cashier's performance to ensure all standards were met.

• Acted as the face of the store in solving all customer service needs.

• Started as cashier in high school promoted to manager upon return in summer after first year of college.

ADDITIONAL LEADERSHIP OR VOLUNTEER EXPERIENCE

Custom Clothing Club, Brandeis University, Waltham, MA
Treasurer, Feb. 2011 – May 2014
President, May 2012 – May 2014

• Built business relationships with clothing business around the country.

• Made sure club continues its mission of providing most affordable customized apparel to all of University.

• Secured the club a total of $13,000 in funding from Brandeis University.

• Maintained a database of all inventory and was in charge of keeping all supplies in stock and planned marketing activities to build recognition of the club in the community.

Language Empowering Action Project, Brandeis University, Waltham, MA

• Trained to teach people of all cultures the English language and improve their reading, writing, and speaking skill.

• Held two hour weekly meetings with member of Waltham Community that I was matched with, and assist them in improving their English skills, to help them better reach their goals.

Zeta Beta Tau Fraternity, Brandeis University, Waltham, MA
Member, Sept. 2010 – May 2014
Risk Management Chair, Jan. 2011 – May 2011

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• Collaborated with eight other members of the Executive Board to successfully lead the chapter.

• Managed the fraternities $15,000 a semester budget.

• Collected all dues from every member and held everyone accountable to individual payment plans.

• Organized fundraising activities for philanthropic organizations.

• Ensured safety of all members of organization and ensuring liability is kept at a minimum.

**Orientation,** Brandeis University, Waltham, MA  
*Orientation Leader,* Aug. 2011

• Led group of 10 freshmen; initiate discussions and activities to ensure their successful transition to college.

• Collaborated with other student leaders to move all incoming students in on Brandeis’ Move-in Day.

• Attended intensive screening and training process to ensure Orientation runs successfully.