Summary
Rheumatoid arthritis (RA) is a chronic, systemic auto-immune disorder characterized by synovial inflammation of the joints and destruction of cartilage and bone. RA patients often present with chronic, symmetric inflammation in the small joints of the hands and feet, although larger joints can be affected too. The inflamed joints are painful, swollen and stiff, and may cause movement restrictions and loss of function. Many patients experience general malaise or fever, and suffer from fatigue, even in periods with limited or no inflammation. In RA, the chronically inflamed synovium may destroy bone tissue. Furthermore, inflamed synovium may produce enzymes that are involved in breakdown of cartilage, which may cause reduced joint space width. Damage of bone, cartilage, and surrounding tissues may cause irreversible joint deformities and loss of function, which may have major impact on physical functioning in daily life. RA is a heterogeneous disease; the course of disease and prognosis varies strongly per patient.

In chapter 1 of this thesis, the general introduction, more information is given about the epidemiology, signs and symptoms, and treatment of RA. The treatment of RA has undergone enormous changes in the last decades due to major scientific insights. Today, treatment is started as soon as possible, during the so-called “window of opportunity”; treatment often consists of combination therapy, with concomitant use of multiple DMARDs; patients are preferably treated according to a “treat-to-target” strategy with the aim to achieve remission rapidly; and patients who experience limited or no effect of treatment with (a combination of) traditional synthetic DMARDs can be treated with bDMARDs and tsDMARDs nowadays: new medicines targeted at specific cytokines, immune cells or intracellular compounds.

Furthermore, chapter 1 provided information about the COBRA-light study, a scientific study in which the effectiveness and safety of COBRA-light therapy (starting with prednisolone 30 mg/day, tapered to 7.5 mg/day in 8 weeks and MTX increased to 25 mg/week in 8 weeks) and COBRA therapy (starting with prednisolone 60 mg/day, tapered to 7.5 mg/day in 6 weeks, MTX 7.5 mg/week and sulfasalazine 2 g/day) were compared in a group of 162 early RA patients. In addition, the first chapter of this thesis elucidated the new ACR/EULAR remission criteria and the importance and role of physical activity in RA. Moreover, the role of body composition (the ratio between FM, FFM, bone mass and body water) in RA, and how to measure body composition accurately in RA are described. Finally, rheumatoid cachexia, a condition of altered, unfavourable body composition in which patients present with an involuntarily loss of FFM and a stable or increased FM, is discussed.

**Part I**

The first part of my thesis describes outcomes of the COBRA-light trial: we studied the efficacy and safety of initial COBRA-light and COBRA therapy over a 4-year follow-up period; the validity of short and sustained periods of ACR/EULAR remission; the longitudinal...
relation between disease activity and physical activity; and the effects of prednisolone
treatment on body composition. Please find below a more detailed overview of each of
the studies.

In chapter 2, we investigated the efficacy and safety of initial COBRA-light versus COBRA
therapy in 149 out of the 162 original trial patients (72 COBRA-light and 77 COBRA patients)
after a 4-year follow-up period. All patients from the original COBRA-light trial were invited
to participate in this COBRA-light extension study, in which they were interviewed and
physically examined, patient reported outcomes were assessed, radiographs were made,
and clinical records were examined for comorbidities and medication use.

The extension study demonstrated that initial COBRA-light and COBRA therapy
have a similar effect on disease activity, physical functioning, radiological outcome and
remission over the 4-year follow-up period. In addition, both treatment groups showed
similar survival and major comorbidities and, besides protocolled differences in use of
prednisolone, methotrexate and sulfasalazine use, similar use of synthetic and biologic
DMARDs and intra-articular and intramuscular glucocorticoid injections over the 4-year
period.

This study demonstrated that early RA patients treated with COBRA-light and COBRA
combination therapy had similar efficacy and safety outcomes over a 4-year follow-up
period, comprising strong and sustained improvements in disease activity and physical
functioning, and good suppression of radiological progression. Therefore, both COBRA-
light and COBRA therapy are effective and safe treatments for early RA patients over a
4-year follow-up period.

In chapter 3, we investigated whether remission in the first year of treatment could predict
good outcome in the second year of treatment. This was studied in a group of 144 early RA
patients, all participants of the COBRA-light trial. The presence of remission was assessed
according to ACR/EULAR and other criteria, and periods of short-term remission during
single visits and sustained periods of remission during consecutive visits were compared.
Good outcome was defined for functional outcome (low HAQ score and no deterioration),
radiographic outcome (no deterioration in SHS), and both (“overall good outcome”).

In the second treatment year, good functional outcome was observed in 35% patients,
good radiographic outcome in 79% patients, and both in 28% of the patients. Patients
who were at least once in remission or sustained remission in the first treatment year
were more likely to experience good functional and good overall outcome in the second
treatment year, than patients who were never in remission in the first treatment year.
Sustained periods of remission were stronger predictors of good outcome during the
second treatment year than remission at single visits. Remission or sustained remission, in
any definition, during the first treatment year was not a predictor of a good radiographic
outcome during the second treatment year.
This study demonstrated that early RA patients who are in remission according to any definition are likely to retain good physical function in the subsequent year; being in remission according to a strict definition, and being in sustained remission both resulted in a stronger prediction of good functional outcome in the subsequent year. In contrast, in the setting of low overall damage progression, (sustained) remission, according to any definition, was not predictive of good radiographic outcome in the subsequent year.

In chapter 4, we investigated the longitudinal relationship between disease activity and physical activity in 140 early RA patients of the COBRA-light trial during their first year of treatment. Physical activity was measured at baseline, and after 13, 26, and 52 weeks, with the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) and reported as the percentage of patients meeting the international guideline for physical activity (150 minutes of moderate-to-intense activity per week).

At baseline, 69% of the patients met the international guideline for physical activity, which increased significantly to 90% at 13 weeks, and stabilized thereafter, with 89% after 1 year. The mean disease activity score improved significantly during the first year from 4.0 to 1.8. Furthermore, disease activity was longitudinally inversely associated with physical activity; a decrease in disease activity was significantly associated with an increase in physical activity. At each time point after baseline, patients with clinically relevant treatment responses (expressed as DAS remission, EULAR good response or ACR 70% improvement score) showed higher levels of physical activity than non-responders, regardless of the definition of response.

This was the first study that demonstrated that combination therapy is not only effective in decreasing disease activity, but also improve self-reported physical activity in early RA patients. This beneficial effect persisted at least one year.

In chapter 5, we investigated the short-term effects of two different high-dose, step-down prednisolone regimens (COBRA-light and COBRA) on body composition in prednisolone- and DMARD-naive, early RA patients. Body composition was assessed with DXA at baseline and after 26 weeks. The sub-group of patients that started treatment after baseline DXA (n=38) was used as primary analysis group.

After 26 weeks of treatment, both treatment groups showed a significant increase of 1.6 kg in total body mass, which was mainly caused by an increase of 1.3 kg in total fat mass. The trunk/peripheral fat ratio and the proportional distribution of total body mass and fat mass did not change over time, and there were no significant differences between the treatment groups.

This study demonstrated that both COBRA-light and COBRA therapy increase total body mass, mainly because of an increase in total fat mass, after 26 weeks of treatment. This may have negative impact on patient health. Yet, we did not demonstrate fat redistribution form peripheral to central tissues, which would have been worse for patient
health. This absence of fat redistribution contradicts the widely held assumption of rapid adverse effects of prednisolone on body composition in RA. Furthermore, the effect of both prednisolone treatments on body composition was not dose-dependent.

Part II
The second part of my thesis focused on the assessment of body composition in RA patients: we studied the relevance of (pre-)cachexia definitions; differences between the assessment of body composition by BMI and BIA; and last but not least: the validity of BIA. Please find below a more detailed overview of each of the studies.

In chapter 6, we investigated the applicability of new consensus definitions of “pre-cachexia” and “cachexia” in a cohort of 103 patients with moderately active RA, mild to moderate disability, and a median disease duration of 8 years. The prevalence of different components of nutritional status and the compiled definitions of “pre-cachexia” and “cachexia” were assessed in a cross-sectional study design by measuring unintentional weight loss, muscle strength, fat-free mass index, appetite, fatigue and inflammatory response.

In this study, 20% of the study population had a low fat-free mass index, and 95% showed decreased muscle strength. Unintentional weight loss and loss of appetite, both essential elements of the newly proposed definitions of (pre-)cachexia, were relative uncommon. Overall, the prevalence of both “pre-cachexia” and “cachexia” was both 1%.

This study demonstrated both impaired body composition and function in a cohort of RA patients. Yet, the new proposed definitions of both “pre-cachexia” and “cachexia” were unable to identify and diagnose impaired nutritional status in this cohort. Both definitions clearly underestimated the diminished nutritional status, as characterized by the individual components. This was mainly because of the low prevalence of both weight loss and decreased appetite.

In chapter 7, we investigated the differences between the assessment of body composition by BMI and BIA in a cohort of 65 patients with moderately active RA, mild to moderate disability, and a median disease duration of 7 years. Single-frequency BIA was used to determine fat-free mass index (FFMI) and fat mass index (FMI) in this study with a cross-sectional study design.

Based on BMI, 2% of the study population were underweight, 45% had a healthy body composition, and 54% were overweight or obese. Based on BIA, which allows to distinguish between FFMI and FMI, 18% had a low FFMI, 55% a normal FFMI, and 26% high of very high FFMI; 26% had a normal FMI, and 74% a high or very high FMI. Low FFMI was found in 44% of the women with a normal BMI. High FMI was found in 40% of the women and 75% of the men with a normal BMI.
This study demonstrated a high frequency of unfavourable body composition, predominantly reduced FFMI and elevated FMI, in a cohort of RA patients. Because of the imbalance between FFMI and FMI, BMI is an unreliable method for the assessment of body composition in RA. BIA might be a more convenient method to assess FFMI and FMI in RA patients in clinical practice, but should be validated first.

In chapter 8, we comment on the article published by Dr. Wolfe and Dr. Michaud, who demonstrated that overweight and obesity in RA patients reduce the risk of mortality, but increase the risk of certain comorbidities. In this study, Wolfe and Michaud used BMI as measure for overweight and obesity.

In our letter to the editor, we emphasized that BMI has limited value for the assessment of body composition in RA patients, since RA patients often present with loss of muscle mass, with little or no weight loss, in the presence of stable or increased fat mass. Since BMI cannot discriminate between muscle and fat mass, it cannot identify abnormal body composition in RA patients, and should not be used when studying the effect of abnormal body composition on mortality in RA.

Furthermore, we suggested to measure FFMI instead of BMI, which has been demonstrated to be useful in identifying patients with decreased muscle mass despite having a normal BMI. FFMI can be assessed by DXA or BIA.

In chapter 9, we compared BIA with two different DXA devices for the assessment of body composition in a group of 43 RA patients, who all participated in the COBRA-light extension-study. In this cross-sectional comparison study, all patients were measured with both a multi-frequency BIA and whole-body DXA at the same day. Patients from study center A (n=25) were scanned with a different DXA device than patients from study center B (n=18).

At individual level, large systematic differences were found for the assessment of absolute and relative fat-free mass and fat mass between DXA and BIA in both study centers. Moreover, the systematic differences found in study center A pointed in the opposite direction as those found in study center B, and limits of agreement were wide, with large absolute differences. At group level, moderate to good agreement was found.

This was the first study in which BIA was compared with two different, widely used DXA devices for the assessment of body composition in RA patients. We demonstrated that BIA might be an inaccurate method for the assessment of body composition in RA patients, especially at individual level. The differences between DXA and BIA were dependent on the DXA device used.