Obesity is a major threat for public health and its study has attracted significant attention in the general population, predominantly due to its association with significant metabolic and cardiovascular complications. In RA research, BMI is frequently reported as a demographical variable, but obesity, as such, has received little interest. This is surprising, in view of the clear associations of obesity with other arthritides, particularly OA, but also in view of the now-clear association of RA with increased cardiovascular morbidity and mortality. In this review, we summarize the studies that have looked into obesity in the RA population, evaluate their findings, identify knowledge gaps and propose directions for future research. We also pose a question of high clinical and research significance: is the use of BMI still a valid way of assessing obesity in RA?

**Key words:** Rheumatoid arthritis, Obesity, Body composition, Body fat, Cachexia, Physical activity, Diet, Lifestyle, Smoking cessation.

RA is a chronic, progressive, autoimmune, inflammatory disease. It mainly affects synovial joints, producing symmetrical arthritis and is characterized by joint pain and stiffness. If left untreated, it leads to irreversible joint damage and deformity, and ultimately disability [4]. RA associates with reduced life expectancy compared with the general population [5], mainly due to increased prevalence of, and worse outcomes from, CVD [6]. The exact cause for this remains unknown; however, genetic predisposition [7–10], classical CVD risk factors [11, 12] and the effects of systemic inflammation on the vasculature [13, 14] are all thought to contribute.

RA also associates with altered body composition. The chronic inflammation of the disease, particularly activation of the nuclear factor kappa-beta (NF-κβ) pathway, trigger metabolic alterations [15] leading to the degradation of lean tissue, especially muscle mass [16]. In combination with inactive lifestyle, this frequently leads to reduced muscle mass in the presence of increased accumulation of body fat (BF) and stable or slightly increased body weight [17], a condition known as rheumatoid cachexia [16]. The study of rheumatoid cachexia has received significant scientific attention as it has a detrimental effect on the morbidity and mortality of RA patients [18]. Nevertheless, there is still no consensus on the exact methods for identifying such patients and the prevalence of rheumatoid cachexia, depending on the method used, ranges from as low as 10% [19] to up to 67% [20]. However, one observation is common to all such studies: rheumatoid cachexia seems to occur almost exclusively in under- and normal-weight individuals; its prevalence...
Body composition and its assessment

Several authors have already discussed this issue extensively both in health and disease [23–29]. The human body is composed of elements; these combine to form molecules and eventually cells. A group of cells forms a tissue and all the tissues together form the body. Thus, body composition can be organized on five levels of increasing complexity: elemental, molecular, cellular, tissue system and whole body [30]. Assessments are available for all different levels (Table 1).

The selection of the method to be used depends largely on the balance between validity, time and money availability. Generally, methods that assess detailed body composition [such as 40K, dual-energy X-ray absorptiometry (DEXA) and MRI] are costly and time consuming, so they are reserved for research in relatively small numbers of individuals. In contrast, anthropometric assessments—such as height, weight, BMI and different circumferences—are cheap, quick and easy to perform, thus frequently used in the clinical setting.

The most common anthropometric assessment for obesity is the BMI (weight divided by height squared). According to World Health Organization (WHO) guidelines [31], individuals with a BMI of >30 kg/m² are classified as obese. They are a distinct category from those with a BMI of 25–30 kg/m², who are characterized as overweight. The importance of BMI lies in its association with CVD risk and overall mortality: overweight individuals have a 20–40% increased mortality rate compared with normal-weight individuals [32].

However, BMI is an index that assesses obesity at the whole-body level; it takes into account total weight but it does not distinguish between different tissues that comprise it. Fat mass and other tissues (i.e. skeletal muscle, bone, organs, skin and blood), collectively known as fat-free mass, are components of total weight and can vary enormously between individuals [24]. In populations with altered body composition, BMI may not be a valid predictor of BF and thus of CVD [17, 33, 34].

Anthropometric measures of central adiposity such as waist circumference and waist to hip ratio have been proposed as alternatives [35–37]. It is suggested that central adiposity is the cause of metabolic disturbances leading to the inclusion of waist circumference in the criteria for the metabolic syndrome [38]. Moreover, it has been suggested that obesity should be redefined based on waist to hip ratio instead of BMI, since this assessment associates with CVD risk in most ethnic groups [39]. However, its predictive strength can be negatively affected by sex and overall body weight in a way that pear-shaped or obese individuals might have optimal waist to hip ratio, but increased overall body weight [40]. More research is necessary to identify the optimal definition of obesity as a predictor for CVD and mortality in the general population and specific subgroups such as the RA population.

The role of adipokines in inflammation

It is now recognized that adipose tissue is not merely an energy storage depot, but an active endocrine/paracrine organ that secretes a number of bioactive molecules called adipokines [41]. It is important to note that the term ‘adipokine’ refers to bioactive molecules found in the adipocytes; however, these might be synthesized at other sites and participate in functions unrelated to the adipose tissue [42]. These have several different functions such as regulation of energy intake and expenditure [43, 44]; however, most of them are also implicated in regulation of inflammation [41]. As a general rule, increased adiposity associates with heightened production of pro-inflammatory molecules, whereas reduced adiposity associates with decreased concentration of pro-inflammatory, and increased concentration of anti-inflammatory molecules; for that reason obesity in now considered a pro-inflammatory state [45].

To date, more than 50 adipokines have been identified [46]. A brief description of the function of the most important adipokines in the inflammatory process is presented in Table 2. Leptin is 16-kDa non-glycosylated peptide hormone encoded by the gene obese, the murine homologue of the human leptin gene [47]. It belongs in the Class I cytokine superfamily and is produced by adipocytes. Its circulating levels are directly correlated with adipose tissue mass and are gender related, with women exhibiting higher levels than men [48]. Its main function is to control energy intake and expenditure, but it also modulates aspects of innate and adaptive immunity towards a pro-inflammatory state [46]. Nevertheless, the exact role of leptin in RA is not clear. Studies have demonstrated both higher [49, 50] and similar [51] levels of leptin in RA patients compared with controls. Similarly, even though an in situ consumption of leptin in the synovium has been suggested [52], studies have shown conflicting results on the association of leptin with RA activity [52–54].

Adiponectin is a 244-residue protein that is produced largely by adipocytes. Its circulating levels drop with

### Table 1: Common assessments for different body composition levels

<table>
<thead>
<tr>
<th>Level</th>
<th>Assessment</th>
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<tbody>
<tr>
<td>Elemental</td>
<td>Neutron activation analysis</td>
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<tr>
<td></td>
<td>Whole-body 40K counting</td>
</tr>
<tr>
<td>Molecular</td>
<td>Under-water weighing</td>
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<tr>
<td></td>
<td>Bio-impedance analysis</td>
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<tr>
<td></td>
<td>DEXA</td>
</tr>
<tr>
<td>Cellular</td>
<td>Tracer dilution</td>
</tr>
<tr>
<td>Tissue system</td>
<td>Computerized axial tomography</td>
</tr>
<tr>
<td></td>
<td>MRI</td>
</tr>
<tr>
<td>Whole body</td>
<td>Anthropometry</td>
</tr>
</tbody>
</table>
increasing weight, while weight loss results in significant increases [55–58]. Adiponectin increases fatty acid oxidation while reducing glucose synthesis in the liver; it has a significant protective role against CVD, insulin resistance and Type II diabetes [59–61]. In RA, circulating adiponectin levels are generally higher than in the general population [49, 62, 63]. In the synovium, RA patients have higher concentrations compared with OA patients [46, 64, 65] even though similar levels between the two populations have also been found [64]. Adiponectin is thought to induce the production of VEGF and MMP in the synovium; it is also implicated in matrix degradation [46, 62, 66, 67]. This suggests a potential role in the pathogenesis of RA for this adipokine; however, a clear link between adiponectin and RA activity is not consistently found [64, 68].

Resistin is a dimeric protein that belongs to the FIZZ (found in inflammatory zones) family; it is present in adipocytes as well as macrophages and other cell types [69]. Its levels have been shown to be increased, decreased or to remain unchanged in human obesity [42, 70, 71], and its initially postulated role as a direct link between obesity and insulin resistance [69, 72] has been challenged by

### Table 2: Association of adipokines with obesity, inflammation, and their potential role in RA

<table>
<thead>
<tr>
<th>Adipokine</th>
<th>Effect of obesity</th>
<th>Effects on inflammation</th>
<th>In RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>↑ Plasma concentration</td>
<td>↑ T-cell activation, ↓ Thymocyte apoptosis, ↑ Thymocyte maturation, ↑ Proliferation and apoptosis of naive T cells, ↓ Proliferation of memory T cells, ↓ Apoptosis of B cells, ↑ Peripheral B-cell pool, ↑ Lymphopoiesis, ↑ Monocyte/macrophage proliferation, phagocytosis and production of IL-1, IL-6, TNF, ↑ IL-1RA, CD25, CD71, ↑ NOS, LTB4, COX2, ↑ Chemotaxis of neutrophils, ↑ Hydrogen peroxide production, ↓ Apoptosis of dendritic cells, ↓ Maturation of dendritic cells and production of Th1, Th2 cytokines, IL-1β, IL-12, IL-6, TNF</td>
<td>↑ or = Probably none</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>↓ Or = plasma concentration</td>
<td>↓ B-cell lymphopoiesis, ↓ T-cell responses, ↓ Phagocytosis, ↓ Endothelial adhesion molecules, ↑ IL-10, IL-1RA, IFN-γ, ↓ TNF, NF-κB, IL-6, ↑ IL-8 (CXCL8) HMW form + LPS</td>
<td>↑ Implicated in RA pathogenesis, Possibly ↑ activity</td>
</tr>
<tr>
<td>Resistin</td>
<td>↑ Or = plasma concentration</td>
<td>↑ Endothelial adhesion molecules, ↑ NF-κB, ↑ IL-1β, IL-12, IL-6, TNF</td>
<td>= ↑ Activity (moderate)</td>
</tr>
<tr>
<td>Visfatin</td>
<td>↑ Plasma concentration</td>
<td>↓ Neutrophil apoptosis, ↑ Chemotaxis, ↑ IL-1RA, IL-1β, IL-8, IL-6, TNF</td>
<td>↑ Potentially ↑ activity</td>
</tr>
</tbody>
</table>

[↑]: increased; [↓]: decreased; =: unchanged; COX2: cyclo-oxygenase 2; HMW: high molecular weight; IgG: immunoglobulin G; IL-1RA: IL-1 receptor antagonist; LPS: lipopolysaccharide; LT4B: leucotriene B4; NOS: nitric oxide synthase.
several authors [70, 73, 74]. In RA, serum resistin levels are comparable with those of healthy controls [49, 75, 76]; however, SF levels are significantly elevated [77]. These positively correlate with synovial leukocyte count and levels of IL-6 [75]; also a moderate association between resistin and disease activity has been suggested [77]. Interestingly, in murine models, injection of resistin into joints triggers an arthritis-like response [75].

Visfatin [initially described as pre-B-cell colony-enhancing factor (PBEF)] is a recently identified adipokine; its circulating levels are directly correlated with increasing adiposity [78, 79]. They are also higher in RA patients compared with healthy controls [49]. To date, very few studies have looked into the potential role of visfatin in RA activity and progression; however, a clear association between visfatin and pro-inflammatory pathways potentially leading to increased disease activity has been described [80]. Of specific interest to the RA population is the recently described link between visfatin and angiogenesis [81], as angiogenesis is highly evident in the rheumatoid synovium [82, 83].

Several other adipokines have the potential to drive RA but research is still very limited. Among these, the two with possibly the greatest potential are vaspin and omentin. The former is elevated in the rheumatoid synovium, while the latter is decreased [80]. However, the way these, or other newly identified adipokines, may affect RA activity is not yet studied.

All the above-described adipokines are implicated in the production of several pro-inflammatory cytokines such as TNF-α and IL-1, IL-6 and the acute-phase reactant CRP. TNF-α is mainly produced by macrophages and lymphocytes; however, it is also found in adipose tissue [84]; its circulating levels increase in obesity [85] and especially in people with abdominal obesity [86]. IL-6 is also secreted from adipocytes [87, 88] and its levels are increased in obesity [89, 90]. One of its functions is to increase CRP production [91]. Until recently, it was thought that CRP production occurs exclusively in the liver; however, newer studies have suggested that it is secreted by several other cells including adipocytes [92–94].

These molecules are directly related to RA activity [95]. TNF-α, IL-1 and IL-6 are central in the pathogenesis and progression of RA as they participate in several steps of the disease including T- and B-cell activation and recruitment, angiogenesis, chemotaxis, vessel permeability and MMP production [96]. TNF-α is responsible to a greater extent for the proliferative and inflammatory aspects of the disease, and IL-1 for the destructive aspects of RA, whereas IL-6 seems to be implicated more in its systemic effects [95]. CRP is the main indicator of disease activity.

The study of obesity in RA

The close associations of obesity both with CVD risk and inflammation, as well as the body composition changes observed in RA patients, render the study of obesity in RA highly significant. Most research in the field of RA has focused on mechanisms causing joint damage and treatments that may prevent disease progression, mainly due to the strong associations of RA with disability [6], but observations and knowledge arising from such work may be directly relevant to further research in obesity and body composition in RA. The cardiovascular aspect of the disease has also attracted attention, with mainly observational studies assessing the associations of RA with CVD risk and outcome [97–100], but although obesity is a significant contributor to CVD in the general population [2], it has received very limited attention in RA. Body weight is routinely assessed in most rheumatology clinics and consistently reported in RA research. However, it is mainly used as a demographic characteristic of the population studied and is usually omitted from further analyses or interpretations. In the few studies that include obesity in their analyses, it is considered as a confounding factor against which data should be corrected and not a primary or even a secondary outcome that could have downstream influences on other aspects of the disease, including comorbidities.

To date, very few studies have addressed obesity as such in RA. This is surprising, as evidence from the general population leads to a very clear hypothesis that obesity could influence RA and its outcome as well as overall health of these patients. However, due to the body composition changes of RA patients it seems likely that the methods used to assess obesity in the general population might not be suitable in RA. We summarize the findings of the few studies investigating obesity in RA, discuss their validity and propose directions for future research in this field.

Definition and prevalence of obesity in RA

Most of the studies assessing body weight in RA use the WHO definition [31] for overweight and obesity. Even though this definition is valid for the general population and can identify individuals at increased CVD risk, it has been proven inaccurate for certain populations with altered body composition. For example, Asian-Indians exhibit increased levels of fat [34], while athletes exhibit increased levels of fat-free mass (i.e. predominantly muscle) [33], for a given BMI. For Asian-Indians, new, lower BMI cut-off points that better identify individuals at increased risk for health complications have been established [34], while for athletes, BMI is no longer considered an accurate measure of CVD risk [33]. As discussed earlier, RA associates with metabolic alterations that lead to reduction in fat-free mass without any obvious change in total body weight; abnormal body composition phenotypes are over-represented in RA patients, especially in those within the ‘normal-weight’ BMI category [21].

Like Asian-Indians, RA patients exhibit reduced fat-free mass for a given BMI and the general (WHO) BMI cut-off points might not be able to identify RA individuals with increased BF [17]. This suggests that the definition of obesity in RA requires an RA-specific approach. Our group performed a study comparing the BMI and
BF of RA patients to that of patients with OA and members of the general population. Our results indicated that for a given BF content, patients with RA had a significantly lower BMI, by almost 2 kg/m², compared with the general population. We have therefore proposed that BMI cut-offs for RA patients should be reduced to 23 and 28 kg/m² for overweight and obesity, respectively [17]. The clinical significance and long-term associations of this recent, RA-specific, definition of obesity remains to be proven.

Similarly, the assessment of central adiposity in RA has been largely ignored. To our knowledge very few studies have evaluated the associations between central adiposity, CVD risk or overall health in RA and most of these treat waist circumference as a component of the metabolic syndrome, not as an indicator of obesity. These studies suggest that increased central adiposity is common in RA [22] and associates with insulin resistance [101] and endothelial dysfunction [102], while it may also associate with increased high-sensitivity CRP levels [103]. We were not able to find any published information on possible associations between central adiposity and morbidity, mortality or disease activity in RA patients. This is an obvious gap in the literature and research in this field could provide helpful information.

The mean BMI reported for RA patients (ranging from 26.5 to 28.2 kg/m²) [17, 104, 105] is similar to that of the general population in the UK (~27.1 kg/m²) [106]. Prevalence of overweight and obesity in RA, as assessed by the general (WHO) BMI cut-off points, appears to be subject to geographical variation. A worldwide study identified 18% of RA patients as obese [107], while a UK-based study found a higher prevalence of 31% [108]. However, in both studies, >60% of RA patients exhibited BMI above the desired levels (>25 kg/m², i.e., were overweight or obese). These results are comparable with those of the general population in the UK where ~35% are overweight and ~25% obese [109]. Results from other studies lie within this range indicating that overweight and obesity, even when assessed based on the general (WHO) BMI cut-offs, are at least as prevalent among RA patients, as they are in the general population [110, 111]. The use of RA-specific BMI cut-off points identify, as expected, an even higher prevalence of overweight (~45%) and obesity (~37%) among RA patients [17]. Probably through a combination of lifestyle change, public health improvements and much more successful RA therapies (not necessarily in this order) the times of the wasted, emaciated RA patient are thankfully mostly gone for good. However, we must not be complacent about what, in many cases, appears to be the opposite extreme, which may also have significant consequences.

**Obesity and RA activity**

Due to the aforementioned close association of obesity with activation of pro-inflammatory pathways, it follows that obese RA patients may have more active and severe disease. However, studies in patients with early RA, of up to 3-year duration, surprisingly suggest that obesity (as assessed by the BMI) may protect against joint damage [119–121]. Similarly, changes in body weight over a 1-year period do not correlate with changes in disease activity during the same period [122]. The protective effect of high BMI seems to be present before the diagnosis of RA, with overweight or obese RA patients exhibiting less joint damage than their normal-weight counterparts at the time of diagnosis [119]; this effect appears to continue during the first few years of RA, with joint damage progressing less rapidly in obese than in normal-weight RA patients [119–121]. Adiponectin concentrations could provide a potential explanation. As discussed earlier, adiponectin might induce disease activity in the joint, resulting in more active disease in lean (i.e., higher adiponectin levels) and less active disease in obese (i.e., lower adiponectin levels) patients [123]. However, it is not entirely clear whether this is indeed a protective effect of obesity against the mechanisms involved in joint degradation in obesity, a reflection of joint damage at the time of first diagnosis or solely an effect of increased weight, for example, through increased mechanical loading stimulating bone synthesis [124], as is indeed the case for osteoporosis in the general population where obesity is suggested to protect against it [125, 126]. This is yet another unexplored area in RA.

In contrast to these observations, studies in unselected (for disease duration) RA patients suggest that obesity associates independently with worse quality of life [127] and with joint-space narrowing in the knees [128]. These indicate that the potential protective effects of obesity in early RA may be diminished or reversed later on in the course of the disease. In one of our studies [129], we found that obese patients with long-standing RA (mean disease duration >10 years) had significantly associated with an odds ratio (OR) for RA of 1.4 (95% CI 1.0, 2.0) [112]. Similarly, in a prospective case-control study of 165 pairs including both genders, obesity was associated with an almost 4-fold (OR 3.74; 95% CI 1.14, 12.27) increase in the risk for developing RA; this association was more pronounced in women (OR 4.96; 95% CI 1.19, 20.71) than men (OR 1.15; 95% CI 0.05, 24.63) [113] and, until recently, some authors still consider obesity as a potential contributor to the development of RA [114]. Newer studies, however, consistently suggest that obesity is not a predisposing factor for RA [115–117] apart from the proportion of RA patients who test negative for anti-CCP antibodies (OR 3.45; 95% CI 1.73, 6.87) [118]. Even though the reason for this discrepancy is not usually discussed, it seems that methodological differences and tight standardization for possible confounders in recent studies eliminate the previous positive findings for the association of obesity with RA development.

**Obesity as a risk factor for the development of RA**

In the first studies to investigate this, obesity was found to associate with increased risk for developing RA. Specifically, in a comparison between 349 incident cases of RA and 1457 controls, obesity in females was
higher disease activity and functional disability than
normal-weight patients, but this was not accompanied
by increased prevalence of erosive disease or joint sur-
gery. It is possible that the previously reported protective
effect of obesity on joint damage could still be present in
long-standing RA patients, but with diminishing influence
over time. Interestingly, all studies suggest a clear asso-
ciation between low BMI and worse disease activity, se-
verity and quality of life. In this case, it is most likely that
significantly reduced BMI is the result rather than the
cause of highly active disease over many years [16].

Overall, it would appear that obesity in RA associates
with higher inflammatory activity, reduced functional
capacity and quality of life, but not increased joint
damage. These are very interesting observations in their
own right, requiring much more in-depth investigation.
The exact impact of adiposity (as in high fat content) vs
obesity (as in high weight) on the acute-phase response
and bone metabolism need to be disentangled, and this
may provide some explanation for the apparent uncou-
pling between the acute-phase response and joint
damage [130]; using BMI as an indicator of obesity is
obviously not sufficient to achieve this. Similarly, obesity
may affect functional capacity and quality of life through
mechanisms independent of the impact of RA itself.

Long-term prospective studies designed specifically for
the purpose are needed to delineate this.

**Obesity and risk for CVD in RA**

Obesity is a well-established, independent risk factor for
CVD in the general population [2]. It is also considered to
be the underlying cause of many other CVD risk factors
such as hypertension, dyslipidaemia and insulin resist-
ance [131] and a potent contributor to the inflammatory
pathogenesis of atherosclerosis [132]. Several studies
have investigated the effects of obesity on CVD risk in
RA, and their results are conflicting.

Obesity independently associates with classical CVD
risk factors in RA [11, 133] and obese RA patients are
more likely to have such risk factors [108]. Therefore,
obesity appears to contribute significantly to an increased
10-year CVD risk event probability of RA patients [134] as
calculated using the Framingham formula [135]. Obesity
is also thought to affect the expression of some pro-inflammatory genes that associate with CVD in RA
[9]. It would therefore be expected that, as in the general
population, obesity would associate with worse cardio-
vascular outcomes in patients with RA. However, RA
patients with low BMI (~18.5 kg/m²) have an even
higher 10-year CVD risk event probability [136]. In ad-
dition, Wolfe and Michaud [137] investigated the effects
of several risk factors and RA medications on the occurrence
of myocardial infarction (MI) in patients with RA: they
concluded that most classical CVD risk factors, but not
obesity, have a significant impact on MI occurrence. In
another study, RA patients with a BMI of &gt;30 kg/m² had
lower all-cause mortality; as BMI decreased, mortality
increased and patients with a low BMI (~20 kg/m²) had
the most significantly increased mortality rates [138].

Quantitative patient questionnaires in standard monitoring
of patients with rheumatoid arthritis (QUEST-RA), a large
multinational study, also found no associations between
obesity and CVD morbidity [107].

These observations are obviously counterintuitive and
there may be several explanations for this. One possibility
is that they are the result of reverse epidemiology, i.e.
paradoxical epidemiological associations between sur-
vival outcomes and traditional CVD risk factors such as
obesity [139]. In diseases associated with accelerated
loss of fat-free mass, such as RA, over-nutrition (a long-
term killer) might protect against the significant health
consequences of reduced fat-free mass while under-
nutrition might enhance muscle wasting and through it
accelerate mortality [140]. However, recent evidence
suggests the same may happen in the general population
[141]: overweight individuals have reduced all-cause
mortality compared with normal-weight individuals, while
the underweight and the morbidly obese are the groups
with the highest mortality rates. Another possibility is that
of analytical deficiencies. In the study of Escalante et al.
[138], the protective effect of BMI was present only when
ESR, a good indicator of disease activity, was low. This
would suggest a significant influence of disease activity on
the way obesity affects CVD in RA, and could bias the
results, as low disease activity associates with higher
fat-free mass [16]. Furthermore, lower disease activity
usually reflects effective therapy, and effective control of
inflammation is also associated with reduced CVD risk
[134]. One exception to this could be steroid treatment.

Even though there are no available data in RA patients,
and our observations did not find any associations
between steroid use and obesity [17], in the general
population use of steroids might result in weight gain.
In addition, the presence of obesity is itself a predictor
of the use of cardio-protective treatment. Obese individ-
uals are significantly more likely to receive medication for
CVD risk modification than their non-obese counterparts
[142, 143]. Smoking could be one more confounder. As is
the case in the general population, RA patients who
smoke have significantly lower BMI and BF compared
with both non-smokers and ex-smokers [144]: lean
smokers face a more acute health threat (i.e. smoking)
compared with obese non-smokers (i.e. obesity). Finally,
the adverse effect of a low BMI mainly reflects the effect
of having a BMI &lt;20 kg/m² [145]. Future research should
aim to account for such potentially important confounders
(i.e. disease activity, RA and CVD medication and smok-
ing), before any conclusions are drawn about the impact
of obesity on CVD in RA patients.

**Causes of obesity and its control**

Since obesity is a very poorly studied subject in RA, its
causes and potential interventions to prevent or reverse it
have received even less scientific attention. In our litera-
ture search, we were able to identify only two studies,
both by our group, looking into factors that might affect
body weight in RA, and two other studies investigating
ways of reducing body weight of patients with RA.
In a cross-sectional study [146], we have compared the relative contributions of physical inactivity, diet and inflammation on BMI and BF in RA patients: obesity associated with low levels of physical activity, and an underweight state associated with low energy intake. Inflammation, even though is suggested to affect body composition in RA, did not appear to associate with either. Another cross-sectional study focused on the effects of smoking on BMI and BF [144]. RA patients who smoked had the lowest BMI, BF and waist circumference, as well as the lowest prevalence of obesity among the participants. In contrast, ex-smokers were those with the highest BMI, BF and waist circumference as well as with the highest prevalence of obesity. These findings are similar to those in the general population [147, 148]. Within the limitations of cross-sectional studies, these findings suggest that lifestyle factors are very important in this context: increasing physical activity is important for obesity control, improving energy intake may prevent an underweight state and smoking cessation should be accompanied by other lifestyle changes to prevent weight and fat accumulation in patients with RA. These need to be addressed in prospective longitudinal studies.

Unfortunately, to our knowledge, there are no widely accepted, validated interventions to control obesity in RA. We were able to identify only two studies that investigated the effects of lifestyle changes on body weight and composition of such patients. In one study, caloric restriction over a period of 12 weeks was used, in combination with a protein-rich diet and low-intensity physical activity. This intervention resulted in modest weight loss (2.7 kg), most of which (1.7 kg) was from reduction in fat-free mass [149]. The other study had a similar design (i.e. 12 weeks of caloric restriction with protein supplementation) but utilized physical activity of moderate intensity. This resulted in a 4.5-kg reduction in body weight with only minimal loss of fat-free mass (<1 kg) [150]. Both studies were relatively small and no safe conclusions can be drawn. Nevertheless, their findings are in line with recent data of studies investigating ways to reverse rheumatoid cachexia. Marcora et al. [151] investigated the effects of 12 weeks of protein supplementation on lean body mass of RA patients. They suggested that increased protein intake can reverse rheumatoid cachexia and significantly increase lean body mass in RA patients, at least in the short term. However, they were not able to find any changes in BF. The same group also investigated the effects of a 12-week resistance exercise intervention on components of rheumatoid cachexia. Lean body mass was again increased as a result of the exercise; interestingly, and even though that was not one of the primary objectives of the trial, total BF was marginally (1.1%) but significantly reduced and trunkal fat also showed a tendency to reduce [152]. It seems therefore that increased protein intake, especially during periods of high disease activity, could protect against losing fat-free mass and ultimately developing rheumatoid cachexia; also that increasing physical activity levels, and especially exercises of higher intensity, are effective in reducing body weight while preserving fat-free mass in RA patients. Such exercise may also decrease CVD risk, as reduced levels of physical activity are directly linked to increased CVD risk in RA [153]. Overall, exercise is known to be safe for RA patients [154] and its potential, as a tool against CVD, has been previously reviewed [155]. However, its effectiveness in the prevention and treatment of obesity needs to be shown in larger prospective studies designed specifically for the purpose.

Conclusions

The limited literature on obesity in RA generates more questions than it answers (Fig. 1). First of all, the WHO definition of overweight and obesity might not be accurate for RA patients; the value of the RA-specific BMI cut-off points proposed by our group remains to be proven in long-term longitudinal studies. Secondly, obesity does not appear to predispose to RA, except possibly anti-CCP-negative RA; the biologic basis of this interesting observation needs to be established. Thirdly, obese RA patients seem to have higher disease activity and worse quality of life but not more joint damage; the exact mechanisms responsible for this apparent dissociation need to be elucidated. Finally, epidemiological work suggests that high BMI might not significantly increase CVD mortality in RA, although several studies associate obesity with CVD risk factors; this is counterintuitive and clearly warrants more research.

However, there is probably a more basic debate to be had: is BMI actually a valid method for assessing obesity? BMI was developed >100 years ago in a society that, in terms of lifestyle, shared very little with the modern way of living [156]. The cut-offs for it were introduced later, but it is in the past couple of decades that obesity has boomed [31, 157, 158]. It is doubtful that obesity is less of a health burden for RA patients than it has been suggested to be in the general population [141]. It is more likely that the inconsistent results obtained using BMI, reflect its inability to actually identify obesity (i.e. increased fat mass).

A possible alternative for the clinical setting would be the use of measures of central adiposity such as waist circumference or waist to hip ratio. Their superiority to BMI is still not proven in the general population [159] and definitely not in RA. Bioelectrical impedance could possibly become a valuable tool for the clinician. It still lacks in validity and reliability compared with other, more advanced, methods but it provides more detailed information, in terms of fat and fat-free mass, compared with anthropometric assessments. Methods such as MRI, DEXA and US should be reserved for research where the detailed analysis of body composition and the sites of fat deposition need to be pursued.

In summary, obesity seems to affect several aspects of the life of RA patients. Clinicians should develop and use disease-specific measures of adiposity, while researchers should focus on the accurate assessment of fat, especially visceral fat, and fat-free mass. The controversy in the findings may well be the result of differing or unsuitable
methodology rather than a true discrepancy in the effects of obesity.

**Rheumatology key messages**
- Obesity is highly prevalent in RA.
- The role of adipokines in RA should be further evaluated.
- Attention should be given to fat mass, fat-free mass and visceral fat.

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