RHEUMATOLOGY

Rheumatology 2011;50:450–462
doi:10.1093/rheumatology/keq266
Advance Access publication 19 October 2010

Review

Obesity in rheumatoid arthritis

Antonios Stavropoulos-Kalinoglou[1,2], Giorgos S. Metsios[1,3], Yiannis Koutedakis[2,4,5] and George D. Kitas[1,6]

Abstract

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.

REVIEW

Introduction

Obesity (from Latin *obēsus* = stout, fat or plump. *Ēsus* is the past participle of *edere* = to eat) [1] is a condition that develops from a chronic quantitative imbalance between energy intake and energy expenditure, leading to accumulation of excessive fat within the body [2]. Obesity has been recognized as a medical condition at least since the time of Hippocrates. He wrote: 'Corpulence is not only a disease itself, but the harbinger of others', recognizing it as a medical disorder in its own right, but also as a disorder with the potential of leading to multiple comorbidities [3]. Obesity is a well-established risk factor for the development of cardiovascular disease (CVD) in the general population and is suggested to be the underlying cause of the metabolic syndrome—a constellation of classical CVD risk factors (such as hypertension, hypercholesterolaemia and hyperinsulinaemia)—which results in a 2- to 3-fold increase in CVD risk [2].

[1]Department of Rheumatology, Dudley Group of Hospitals NHS Trust, Russell's Hall Hospital, Dudley, [2]School of Sports and Exercise Science, University of Birmingham, Edgbaston, [3]School of Sport, Performing Arts and Leisure, University of Wolverhampton, Wolverhampton, UK, [4]Department of Sport and Exercise Science, University of Thessaly, [5]Institute of Human Performance and Rehabilitation, Trikala, Greece and [6]ARC Epidemiology Unit, University of Manchester, Manchester, UK.

Submitted 7 July 2009; revised version accepted 12 July 2010.

Correspondence to: Antonios Stavropoulos-Kalinoglou, Department of Rheumatology, Dudley Group of Hospitals NHS Trust, Russells Hall Hospital, Pensnett Road, Dudley DY1 2HQ, UK. E-mail: a.stavropoulos kalinoglou@bham.ac.uk

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

decreases as weight increases, and it effectively does not exist in the obese [21, 22]. Thus, although both obesity and rheumatoid cachexia are clearly related to body composition, they are different entities and as such require separate attention and study.

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 ^{40}K, 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/m^2 are classified as obese. They are a distinct category from those with a BMI of 25–30 kg/m^2, 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%, while obese a 2- to 3-fold 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.

Table 1 Common assessments for different body composition levels

Level	Assessment
Elemental	Neutron activation analysis
	Whole-body ^{40}K counting
Molecular	Under-water weighing
	Bio-impedance analysis
	DEXA
Cellular	Tracer dilution
Tissue system	Computerized axial tomography
	MRI
	US
Whole body	Anthropometry

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

Adipokine	Effect of obesity	Effects on inflammation	In RA	
			Levels	Effects on disease activity
Leptin	↑ Plasma concentration	↑ 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 T_H1, T_H2 cytokines, IL-1β, IL-12, IL-6, TNF ↑ Survival and cytotoxicity of NK cells	↑↓ or =	Probably none
Adiponectin	↓ Plasma concentration	↓ 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	↑	Implicated in RA pathogenesis Possibly ↑ activity
Resistin	↑↓ Or = plasma concentration	↑ Endothelial adhesion molecules ↑ NF-κB ↑ IL-1β, IL-12, IL-6, TNF	=	↑ Activity (moderate)
Visfatin	↑ Plasma concentration	↓ Neutrophil apoptosis ↑ Chemotaxis ↑ IL-1RA, IL-1β, IL-8, IL-6, TNF	↑	Potentially ↑ activity

[↑]: increased; [↓]: decreased; =: unchanged; COX2: cyclo-oxygenase 2; HMW: high molecular weight; IgG: immunoglobulin G; IL-1RA: IL-1 receptor antagonist; LPS: lipopolysaccharide; LTB4: leucotriene B4; NOS: nitric oxide synthase.

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

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 leucocyte 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 recruitment and activation, 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 demographical 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 overrepresented 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/m^2, compared with the general population. We have therefore proposed that BMI cut-offs for RA patients should be reduced to 23 and 28 kg/m^2 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/m^2) [17, 104, 105] is similar to that of the general population in the UK (~27.1 kg/m^2) [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 (>25kg/m^2, 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 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 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 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 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

higher disease activity and functional disability than normal-weight patients, but this was not accompanied by increased prevalence of erosive disease or joint surgery. 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 association between low BMI and worse disease activity, severity 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 uncoupling 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 resistance [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 cardiovascular outcomes in patients with RA. However, RA patients with low BMI ($<18.5\,kg/m^2$) have an even higher 10-year CVD risk event probability [136]. In addition, 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 $>30\,kg/m^2$ had lower all-cause mortality; as BMI decreased, mortality increased and patients with a low BMI ($<20\,kg/m^2$) 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 survival 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 results in weight gain. In addition, the presence of obesity is itself a predictor of the use of cardio-protective treatment. Obese individuals 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 $<20\,kg/m^2$ [145]. Future research should aim to account for such potentially important confounders (i.e. disease activity, RA and CVD medication and smoking), 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 literature 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

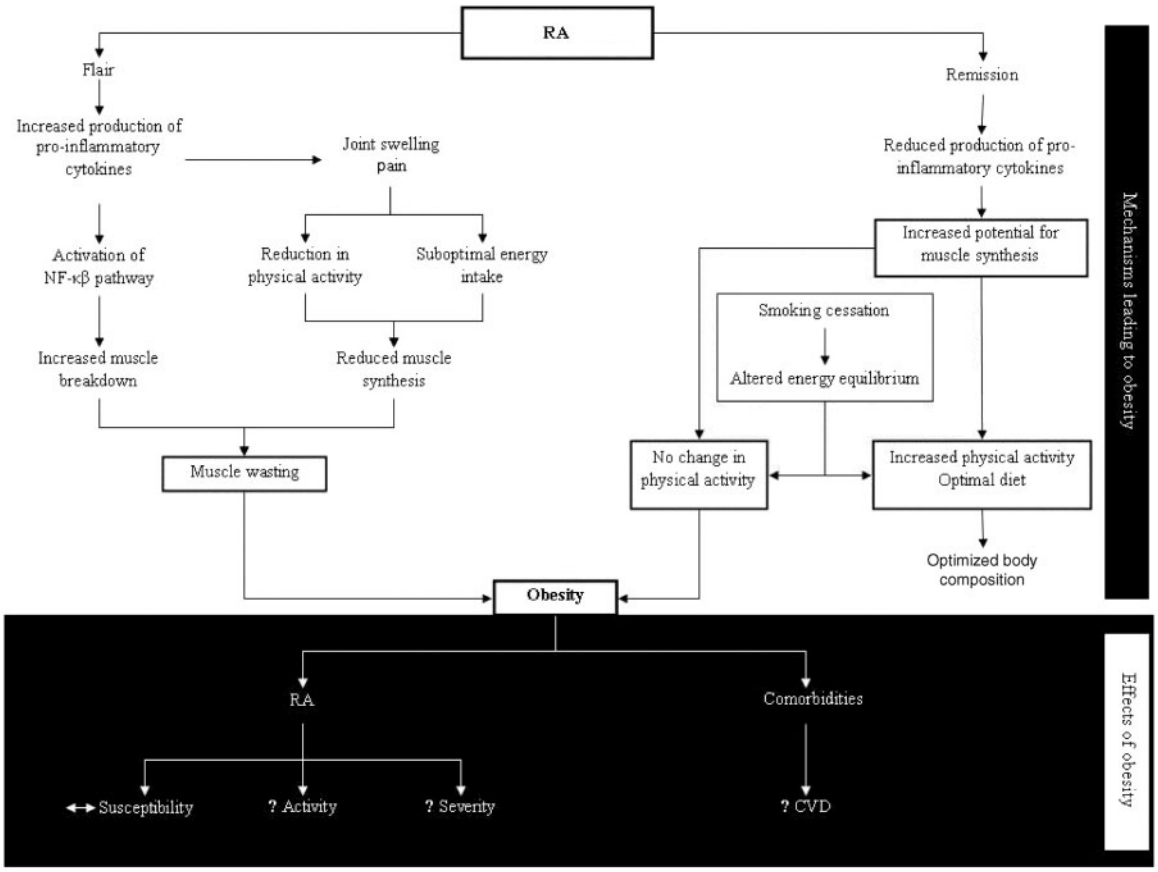
The limited literature on obesity in RA generates more questions than it answers (Fig. 1). First of all, the WHO definition of overweight and obesity might not be accurate for RA patients; the value of the RA-specific BMI cut-off points proposed by our group remains to be proven in long-term longitudinal 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

Fig. 1 Possible pathways leading to obesity and health aspects obesity might affect in RA. During periods of high disease activity, inflammation leads to increased muscle breakdown, reduced levels of physical activity and suboptimal energy intake enhancing muscle wasting. During periods of low disease activity, if patients increase physical activity levels and optimize their diet, muscle wasting can be reversed and fat storage minimized. Otherwise, if physical activity remains at low levels, obesity might develop. The 'black' area of the health consequences of obesity in RA requires further study with the use of RA-specific measures of adiposity. Question marks indicate uncertainties in this area. ↔: unchanged.



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.

Acknowledgements

Funding: This study was funded by the Dudley Group of Hospitals R&D directorate cardiovascular programme grant and a Wolverhampton University equipment grant. The Department of Rheumatology has an infrastructure support grant from the Arthritis Research Campaign (number: 17682).

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

References

1 Onions CT, Friedrichsen GWS, Burchfield RW. The Oxford dictionary of English etymology. Oxford, UK: Oxford University Press, 1996.

2 Bray GA, Bellanger T. Epidemiology, trends, and morbidities of obesity and the metabolic syndrome. Endocrine 2006;29:109–17.

3 Haslam DW, James WP. Obesity. Lancet 2005;366:1197–209.

4 Emery P, Foster W, Suarez-Almazor M. Rheumatoid arthritis. Clin Evid 2002;1101–21.

5 Erhardt CC, Mumford PA, Venables PJ, Maini RN. Factors predicting a poor life prognosis in rheumatoid arthritis: an

eight year prospective study. Ann Rheum Dis 1989;48:7–13.

6 Kitas GD, Erb N. Tackling ischaemic heart disease in rheumatoid arthritis. Rheumatology 2003;42:607–13.

7 Gonzalez-Gay MA, Gonzalez-Juanatey C, Lopez-Diaz MJ *et al*. HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. Arthritis Rheum 2007;57:125–32.

8 Panoulas VF, Nikas SN, Smith JP *et al*. Lymphotoxin 252A>G polymorphism is common and associates with myocardial infarction in patients with rheumatoid arthritis. Ann Rheum Dis 2008;67:1550–6.

9 Panoulas VF, Stavropoulos-Kalinoglou A, Metsios GS *et al*. Association of interleukin-6 (IL-6)-174G/C gene polymorphism with cardiovascular disease in patients with rheumatoid arthritis: the role of obesity and smoking. Atherosclerosis 2009;204:178–83.

10 Mattey DL, Dawes PT, Nixon NB, Goh L, Banks MJ, Kitas GD. Increased levels of antibodies to cytokeratin 18 in patients with rheumatoid arthritis and ischaemic heart disease. Ann Rheum Dis 2004;63:420–5.

11 Panoulas VF, Douglas KM, Milionis HJ *et al*. Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis. Rheumatology 2007;46:1477–82.

12 Toms TE, Panoulas VF, Douglas KM, Griffiths HR, Kitas GD. Lack of association between glucocorticoid use and presence of the metabolic syndrome in patients with rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther 2008;10:R145.

13 Stevens RJ, Douglas KM, Saratzis AN, Kitas GD. Inflammation and atherosclerosis in rheumatoid arthritis. Expert Rev Mol Med 2005;7:1–24.

14 Gonzalez A, Kremers HM, Crowson CS *et al*. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients? Ann Rheum Dis 2008;67:64–9.

15 Metsios GS, Stavropoulos-Kalinoglou A, Panoulas VF *et al*. New resting energy expenditure prediction equations for patients with rheumatoid arthritis. Rheumatology 2008;47:500–6.

16 Roubenoff R, Roubenoff RA, Cannon JG *et al*. Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. J Clin Invest 1994;93:2379–86.

17 Stavropoulos-Kalinoglou A, Metsios GS, Koutedakis Y *et al*. Redefining overweight and obesity in rheumatoid arthritis patients. Ann Rheum Dis 2007;66:1316–21.

18 Kremers HM, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. Arthritis Rheum 2004;50:3450–7.

19 Morley JE, Thomas DR, Wilson MM. Cachexia: pathophysiology and clinical relevance. Am J Clin Nutr 2006;83:735–43.

20 Roubenoff R, Roubenoff RA, Ward LM, Holland SM, Hellmann DB. Rheumatoid cachexia: depletion of lean body mass in rheumatoid arthritis. Possible association with tumor necrosis factor. J Rheumatol 1992;19:1505–10.

21 Giles JT, Ling SM, Ferrucci L *et al*. Abnormal body composition phenotypes in older rheumatoid arthritis patients: association with disease characteristics and pharmacotherapies. Arthritis Rheum 2008;59:807–15.

22 Elkan AC, Engvall IL, Cederholm T, Hafstrom I. Rheumatoid cachexia, central obesity and malnutrition in patients with low-active rheumatoid arthritis: feasibility of anthropometry, mini nutritional assessment and body composition techniques. Eur J Nutr 2009;48:315–22.

23 Ellis KJ. Human body composition: in vivo methods. Physiol Rev 2000;80:649–80.

24 Mattsson S, Thomas BJ. Development of methods for body composition studies. Phys Med Biol 2006;51:R203–28.

25 Sutcliffe JF. A review of in vivo experimental methods to determine the composition of the human body. Phys Med Biol 1996;41:791–833.

26 Summers GD, Deighton CM, Rennie MJ, Booth AH. Rheumatoid cachexia: a clinical perspective. Rheumatology 2008;47:1124–31.

27 Levitt DG, Heymsfield SB, Pierson RN Jr, Shapses SA, Kral JG. Physiological models of body composition and human obesity. Nutr Metab 2009;6:7.

28 Lee SY, Gallagher D. Assessment methods in human body composition. Curr Opin Clin Nutr Metab Care 2008;11:566–72.

29 Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: advances in models and methods. Annu Rev Nutr 1997;17:527–58.

30 Wang Z, Pierson R Jr, Heymsfield S. The five-level model: a new approach to organizing body-composition research. Am J Clin Nutr 1992;56:19–28.

31 World Health Organisation. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. World Health Organ Tech Rep Ser 2000;894:i–xii:1–253.

32 Adams KF, Schatzkin A, Harris TB *et al*. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med 2006;355:763–78.

33 Nevill AM, Stewart AD, Olds T, Holder R. Are adult physiques geometrically similar? The dangers of allometric scaling using body mass power laws. Am J Phys Anthropol 2004;124:177–82.

34 World Health Organisation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–63.

35 Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. Am J Clin Nutr 2004;79:379–84.

36 Dalton M, Cameron AJ, Zimmet PZ *et al*. Waist circumference, waist-hip ratio and body mass index and their correlation with cardiovascular disease risk factors in Australian adults. J Intern Med 2003;254:555–63.

37 Janssen I, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health Guidelines. Arch Intern Med 2002;162:2074–9.

38 Alberti KGM, Zimmet P, Shaw J. The metabolic syndrome–a new worldwide definition. Lancet 2005;366:1059–62.

39 Yusuf S, Hawken S, Ounpuu S *et al*. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet 2005;366:1640–9.

40 Li C, Engstrom G, Hedblad B, Calling S, Berglund G, Janzon L. Sex differences in the relationships between BMI, WHR and incidence of cardiovascular disease: a population-based cohort study. Int J Obes 2006;30: 1775–81.

41 Mohamed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. Int J Obes Relat Metab Disord 1998;22:1145–58.

42 Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 2005;115:911–9; quiz 920.

43 Houseknecht KL, Baile CA, Matteri RL, Spurlock ME. The biology of leptin: a review. J Anim Sci 1998;76: 1405–20.

44 Chandran M, Phillips SA, Ciaraldi T, Henry RR. Adiponectin: more than just another fat cell hormone? Diabetes Care 2003;26:2442–50.

45 Ramos EJB, Xu Y, Romanova I *et al*. Is obesity an inflammatory disease? Surgery 2003;134:329–35.

46 Lago F, Dieguez C, Gomez-Reino J, Gualillo O. Adipokines as emerging mediators of immune response and inflammation. Nat Clin Pract Rheumatol 2007;3:716–24.

47 Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372:425–32.

48 Otero M, Lago R, Gomez R *et al*. Towards a pro-inflammatory and immunomodulatory emerging role of leptin. Rheumatology 2006;45:944–50.

49 Otero M, Lago R, Gomez R *et al*. Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. Ann Rheum Dis 2006;65:1198–201.

50 Rho YH, Solus J, Sokka T *et al*. Adipocytokines are associated with radiographic joint damage in rheumatoid arthritis. Arthritis Rheum 2009;60:1906–14.

51 Toussirot E, Streit G, Wendling D. The contribution of adipose tissue and adipokines to inflammation in joint diseases. Curr Med Chem 2007;14:1095–100.

52 Bokarewa M, Bokarew D, Hultgren O, Tarkowski A. Leptin consumption in the inflamed joints of patients with rheumatoid arthritis. Ann Rheum Dis 2003;62:952–6.

53 Seven A, Guzel S, Aslan M, Hamuryudan V. Serum and synovial fluid leptin levels and markers of inflammation in rheumatoid arthritis. Rheumatol Int 2009;29:743–7.

54 Hizmetli S, Kisa M, Gokalp N, Bakici MZ. Are plasma and synovial fluid leptin levels correlated with disease activity in rheumatoid arthritis? Rheumatol Int 2007;27:335–8.

55 Oh DK, Ciaraldi T, Henry RR. Adiponectin in health and disease. Diabetes Obes Metab 2007;9:282–9.

56 Esposito K, Pontillo A, Di Palo C *et al*. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. JAMA 2003;289: 1799–804.

57 Kopp HP, Krzyzanowska K, Mohlig M, Spranger J, Pfeiffer AF, Schernthaner G. Effects of marked weight loss on plasma levels of adiponectin, markers of chronic subclinical inflammation and insulin resistance in morbidly obese women. Int J Obes 2005;29:766–71.

58 Yang WS, Lee WJ, Funahashi T *et al*. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. J Clin Endocrinol Metab 2001;86:3815–9.

59 Yamauchi T, Kamon J, Waki H *et al*. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001;7:941–6.

60 Lam KS, Xu A. Adiponectin: protection of the endothelium. Curr Diab Rep 2005;5:254–9.

61 Weyer C, Funahashi T, Tanaka S *et al*. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001;86:1930–5.

62 Schaffler A, Ehling A, Neumann E *et al*. Adipocytokines in synovial fluid. JAMA 2003;290:1709–10.

63 Gonzalez-Gay MA, Llorca J, Garcia-Unzueta MT *et al*. High-grade inflammation, circulating adiponectin concentrations and cardiovascular risk factors in severe rheumatoid arthritis. Clin Exp Rheumatol 2008;26: 596–603.

64 Senolt L, Pavelka K, Housa D, Haluzik M. Increased adiponectin is negatively linked to the local inflammatory process in patients with rheumatoid arthritis. Cytokine 2006;35:247–52.

65 Choi HM, Lee YA, Lee SH *et al*. Adiponectin may contribute to synovitis and joint destruction in rheumatoid arthritis by stimulating vascular endothelial growth factor, matrix metalloproteinase-1, and matrix metalloproteinase-13 expression in fibroblast-like synoviocytes more than proinflammatory mediators. Arthritis Res Ther 2009;11:R161.

66 Ehling A, Schaffler A, Herfarth H *et al*. The potential of adiponectin in driving arthritis. J Immunol 2006;176: 4468–78.

67 Gomez R, Lago F, Gomez-Reino J, Dieguez C, Gualillo O. Adipokines in the skeleton: influence on cartilage function and joint degenerative diseases. J Mol Endocrinol 2009; 43:11–8.

68 Harle P, Sarzi-Puttini P, Cutolo M, Straub RH. No change of serum levels of leptin and adiponectin during anti-tumour necrosis factor antibody treatment with adalimumab in patients with rheumatoid arthritis. Ann Rheum Dis 2006;65:970–1.

69 Steppan CM, Bailey ST, Bhat S *et al*. The hormone resistin links obesity to diabetes. Nature 2001;409:307–12.

70 Degawa-Yamauchi M, Bovenkerk JE, Juliar BE *et al*. Serum resistin (FIZZ3) protein is increased in obese humans. J Clin Endocrinol Metab 2003;88:5452–5.

71 Pagano C, Marin O, Calcagno A *et al*. Increased serum resistin in adults with Prader-Willi syndrome is related to obesity and not to insulin resistance. J Clin Endocrinol Metab 2005;90:4335–40.

72 McTernan CL, McTernan PG, Harte AL, Levick PL, Barnett AH, Kumar S. Resistin, central obesity, and type 2 diabetes. Lancet 2002;359:46–7.

73 Janke J, Engeli S, Gorzelniak K, Luft FC, Sharma AM. Resistin gene expression in human adipocytes is not related to insulin resistance. Obes Res 2002;10:1–5.

74 Lee JH, Chan JL, Yiannakouris N *et al*. Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-sectional and interventional studies in normal, insulin-resistant, and diabetic Subjects. J Clin Endocrinol Metab 2003;88:4848–56.

75 Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. J Immunol 2005;174:5789–95.

76 Pang SS, Le YY. Role of resistin in inflammation and inflammation-related diseases. Cell Mol Immunol 2006;3: 29–34.

77 Senolt L, Housa D, Vernerova Z *et al*. Resistin in rheumatoid arthritis synovial tissue, synovial fluid and serum. Ann Rheum Dis 2007;66:458–63.

78 Chen MP, Chung FM, Chang DM *et al*. Elevated plasma level of visfatin/pre-B cell colony-enhancing factor in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 2006;91:295–9.

79 Berndt J, Kloting N, Kralisch S *et al*. Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. Diabetes 2005;54:2911–6.

80 Brentano F, Schorr O, Ospelt C *et al*. Pre-B cell colony-enhancing factor/visfatin, a new marker of inflammation in rheumatoid arthritis with proinflammatory and matrix-degrading activities. Arthritis Rheum 2007;56: 2829–39.

81 Adya R, Tan BK, Punn A, Chen J, Randeva HS. Visfatin induces human endothelial VEGF and MMP-2/9 production via MAPK and PI3K/Akt signalling pathways: novel insights into visfatin-induced angiogenesis. Cardiovasc Res 2008;78:356–65.

82 Firestein GS. Starving the synovium: angiogenesis and inflammation in rheumatoid arthritis. J Clin Invest 1999; 103:3–4.

83 Paleolog E, Fava R. Angiogenesis in rheumatoid arthritis: implications for future therapeutic strategies. Springer Semin Immunopathol 1998;20:73–94.

84 Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;259: 87–91.

85 Zinman B, Hanley AJ, Harris SB, Kwan J, Fantus IG. Circulating tumor necrosis factor-alpha concentrations in a native Canadian population with high rates of type 2 diabetes mellitus. J Clin Endocrinol Metab 1999;84: 272–8.

86 Tsigos C, Kyrou I, Chala E *et al*. Circulating tumor necrosis factor alpha concentrations are higher in abdominal versus peripheral obesity. Metabolism 1999;48: 1332–5.

87 Crichton MB, Nichols JE, Zhao Y, Bulun SE, Simpson ER. Expression of transcripts of interleukin-6 and related cytokines by human breast tumors, breast cancer cells, and adipose stromal cells. Mol Cell Endocrinol 1996;118: 215–20.

88 Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab 2001;280:E745–51.

89 Roytblat L, Rachinsky M, Fisher A *et al*. Raised interleukin-6 levels in obese patients. Obes Res 2000;8: 673–5.

90 Eder K, Baffy N, Falus A, Fulop A. The major inflammatory mediator interleukin-6 and obesity. Inflamm Res 2009;58: 727–36.

91 Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. Biochem J 1990;265:621–36.

92 Calabro P, Chang DW, Willerson JT, Yeh ET. Release of C-reactive protein in response to inflammatory cytokines by human adipocytes: linking obesity to vascular inflammation. J Am Coll Cardiol 2005;46:1112–3.

93 Ouchi N, Kihara S, Funahashi T *et al*. Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. Circulation 2003;107:671–4.

94 Anty R, Bekri S, Luciani N *et al*. The inflammatory C-reactive protein is increased in both liver and adipose tissue in severely obese patients independently from metabolic syndrome, type 2 diabetes, and NASH. Am J Gastroenterol 2006;101:1824–33.

95 Buch M, Emery P. The aetiology and pathogenesis of rheumatiod arthritis. Hospital Pharmacist 2002;9:5–10.

96 Klimiuk PA, Goronzy JJ, Bjornsson J, Beckenbaugh RD, Weyand CM. Tissue cytokine patterns distinguish variants of rheumatoid synovitis. Am J Pathol 1997;151: 1311–9.

97 Douglas KM, Pace AV, Treharne GJ *et al*. Excess recurrent cardiac events in rheumatoid arthritis patients with acute coronary syndrome. Ann Rheum Dis 2006;65: 348–53.

98 Cobb S, Anderson F, Bauer W. Length of life and cause of death in rheumatoid arthritis. N Engl J Med 1953;249: 553–6.

99 Goodson N. Coronary artery disease and rheumatoid arthritis. Curr Opin Rheumatol 2002;14:115–20.

100 van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis An extraarticular feature of rheumatoid arthritis? Arthritis Rheum 2002;46:862–73.

101 Dessein PH, Joffe BI. Insulin resistance and impaired beta cell function in rheumatoid arthritis. Arthritis Rheum 2006;54:2765–75.

102 Dessein PH, Joffe BI, Singh S. Biomarkers of endothelial dysfunction, cardiovascular risk factors and atherosclerosis in rheumatoid arthritis. Arthritis Res Ther 2005;7:R634–43.

103 Dessein PH, Stanwix AE, Joffe BI. Cardiovascular risk in rheumatoid arthritis versus osteoarthritis: acute phase response related decreased insulin sensitivity and high-density lipoprotein cholesterol as well as clustering of metabolic syndrome features in rheumatoid arthritis. Arthritis Res 2002;4:R5.

104 Saravana S, Gillott T. Ischaemic heart disease in rheumatoid arthritis patients. Rheumatology 2004;43: 1134; author reply 114.

105 Gordon MM, Thomson EA, Madhok R, Capell HA. Can intervention modify adverse lifestyle variables in a rheumatoid population? Results of a pilot study. Ann Rheum Dis 2002;61:66–9.

106 The Information Centre for Health and Social Care. Health Survey for England. London: Department of Health, 2005.

107 Naranjo A, Sokka T, Descalzo MA *et al*. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther 2008;10:R30.

108 Armstrong DJ, McCausland EM, Quinn AD, Wright GD. Obesity and cardiovascular risk factors in rheumatoid arthritis. Rheumatology 2006;45:782author reply 782–3.

109 Zaninotto P, Wardle H, Stamatakis E, Mindell J, Head J. Forecasting obesity to 2010. London: Department of Health, 2006.

110 Gordon MM, Capell HA, Madhok R. The use of the internet as a resource for health information among patients attending a rheumatology clinic. Rheumatology 2002;41:1402–5.

111 Zonana-Nacach A, Santana-Sahagun E, Jimenez-Balderas FJ, Camargo-Coronel A. Prevalence and factors associated with metabolic syndrome in patients with rheumatoid arthritis and systemic lupus erythematosus. J Clin Rheumatol 2008;14:74–7.

112 Voigt LF, Koepsell TD, Nelson JL, Dugowson CE, Daling JR. Smoking, obesity, alcohol consumption, and the risk of rheumatoid arthritis. Epidemiology 1994;5: 525–32.

113 Symmons DP, Bankhead CR, Harrison BJ *et al*. Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: results from a primary care-based incident case-control study in Norfolk, England. Arthritis Rheum 1997;40:1955–61.

114 Symmons DP. Looking back: rheumatoid arthritis–aetiology, occurrence and mortality. Rheumatology 2005;44(Sup)pl).) 4):iv14–7.

115 Cerhan JR, Saag KG, Criswell LA, Merlino LA, Mikuls TR. Blood transfusion, alcohol use, and anthropometric risk factors for rheumatoid arthritis in older women. J Rheumatol 2002;29:246–54.

116 Bartfai T, Waalen J, Buxbaum JN. Adipose tissue as a modulator of clinical inflammation: does obesity reduce the prevalence of rheumatoid arthritis? J Rheumatol 2007;34:488–92.

117 Rodriguez LA, Tolosa LB, Ruigomez A, Johansson S, Wallander MA. Rheumatoid arthritis in UK primary care: incidence and prior morbidity. Scand J Rheumatol 2009; 38:173–7.

118 Pedersen M, Jacobsen S, Klarlund M *et al*. Environmental risk factors differ between rheumatoid arthritis with and without auto-antibodies against cyclic citrullinated peptides. Arthritis Res Ther 2006;8: R133.

119 Westhoff G, Rau R, Zink A. Radiographic joint damage in early rheumatoid arthritis is highly dependent on body mass index. Arthritis Rheum 2007;56:3575–82.

120 van der Helm-van Mil AHM, van der Kooij SM, Allaart CF, Toes REM, Huizinga TWJ. A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis. Ann Rheum Dis 2008;67:769–74.

121 Kaufmann J, Kielstein V, Kilian S, Stein G, Hein G. Relation between body mass index and radiological progression in patients with rheumatoid arthritis. J Rheumatol 2003;30:2350–5.

122 Morgan SL, Anderson AM, Hood SM, Matthews PA, Lee JY, Alarcon GS. Nutrient intake patterns, body mass index, and vitamin levels in patients with rheumatoid arthritis. Arthritis Care Res 1997;10:9–17.

123 Giles JT, Allison M, Bingham CO 3rd, Scott WM Jr, Bathon JM. Adiponectin is a mediator of the inverse association of adiposity with radiographic damage in rheumatoid arthritis. Arthritis Rheum 2009;61:1248–56.

124 Tremollieres FA, Pouilles JM, Ribot C. Vertebral post-menopausal bone loss is reduced in overweight women: a longitudinal study in 155 early postmenopausal women. J Clin Endocrinol Metab 1993;77:683–6.

125 Barrera G, Bunout D, Gattas V, de la Maza MP, Leiva L, Hirsch S. A high body mass index protects against femoral neck osteoporosis in healthy elderly subjects. Nutrition 2004;20:769–71.

126 Zhao LJ, Liu YJ, Liu PY, Hamilton J, Recker RR, Deng HW. Relationship of obesity with osteoporosis. J Clin Endocrinol Metab 2007;92:1640–6.

127 Garcia-Poma A, Segami MI, Mora CS *et al*. Obesity is independently associated with impaired quality of life in patients with rheumatoid arthritis. Clin Rheumatol 2007; 26:1831–5.

128 Hollingworth P, Melsom RD, Scott JT. Measurement of radiographic joint space in the rheumatoid knee: correlation with obesity, disease duration, and other factors. Rheumatol Rehabil 1982;21:9–14.

129 Stavropoulos-Kalinoglou A, Metsios GS *et al*. Underweight and obese states both associate with worse disease activity and physical function in patients with established rheumatoid arthritis. Clin Rheumatol 2009;28:439–44.

130 Smolen JS, Van Der Heijde DMFM, St Clair EW *et al*. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. Arthritis Rheum 2006;54: 702–10.

131 Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433–8.

132 Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. Circ Res 2005;96:939–49.

133 Stavropoulos-Kalinoglou A, Metsios GS, Panoulas VF *et al*. Associations of obesity with modifiable risk factors for the development of cardiovascular disease in patients with rheumatoid arthritis. Ann Rheum Dis 2009; 68:242–5.

134 Kremers HM, Crowson CS, Therneau TM, Roger VL, Gabriel SE. High ten-year risk of cardiovascular disease in newly diagnosed rheumatoid arthritis patients: a population-based cohort study. Arthritis Rheum 2008; 58:2268–74.

135 Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. Circulation 1991;83:356–62.

136 Kremer JM. Rational use of new and existing disease-modifying agents in rheumatoid arthritis. Ann Intern Med 2001;134:695–706.

137 Wolfe F, Michaud K. The risk of myocardial infarction and pharmacologic and nonpharmacologic myocardial infarction predictors in rheumatoid arthritis: a cohort and nested case-control analysis. Arthritis Rheum 2008;58: 2612–21.

138 Escalante A, Haas RW, del Rincon I. Paradoxical effect of body mass index on survival in rheumatoid arthritis: role of comorbidity and systemic inflammation. Arch Intern Med 2005;165:1624–9.

139 Horwich TB, Fonarow GC. Reverse epidemiology beyond dialysis patients: chronic heart failure, geriatrics, rheumatoid arthritis, COPD, and AIDS. Semin Dial 2007; 20:549–53.

140 Kalantar-Zadeh K, Horwich TB, Oreopoulos A *et al*. Risk factor paradox in wasting diseases. Curr Opin Clin Nutr Metab Care 2007;10:433–42.

141 Romero-Corral A, Montori VM, Somers VK *et al*. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet 2006;368: 666–78.

142 Chobanian AV, Bakris GL, Black HR *et al*. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–52.

143 Narbro K, Agren G, Jonsson E, Naslund I, Sjostrom L, Peltonen M. Pharmaceutical costs in obese individuals: comparison with a randomly selected population sample and long-term changes after conventional and surgical treatment: the SOS intervention study. Arch Intern Med 2002;162:2061–9.

144 Stavropoulos-Kalinoglou A, Metsios GS, Panoulas VF *et al*. Cigarette smoking associates with body weight and muscle mass of patients with rheumatoid arthritis: a cross-sectional, observational study. Arthritis Res Ther 2008;10:R59.

145 Hall FC, Dalbeth N. Re: obesity and cardiovascular risk factors in rheumatoid arthritis. Rheumatology 2006;45: 782–3.

146 Stavropoulos-Kalinoglou A, Metsios GS, Smith JP *et al*. What predicts obesity in patients with rheumatoid arthritis? An investigation of the interactions between lifestyle and inflammation. Int J Obes 2010;34: 295–301.

147 Filozof C, Pinilla MCF, Fernández-Cruz A. Smoking cessation and weight gain. Obes Rev 2004;5:95–103.

148 Froom P, Melamed S, Benbassat J. Smoking cessation and weight gain. J Fam Pract 1998;46:460–4.

149 Heitmann BL, Kondrup J, Engelhart M *et al*. Changes in fat free mass in overweight patients with rheumatoid arthritis on a weight reducing regimen. A comparison of eight different body composition methods. Int J Obes Relat Metab Disord 1994;18:812–9.

150 Engelhart M, Kondrup J, Hoie LH, Andersen V, Kristensen JH, Heitmann BL. Weight reduction in obese patients with rheumatoid arthritis, with preservation of body cell mass and improvement of physical fitness. Clin Exp Rheumatol 1996;14:289–93.

151 Marcora S, Lemmey A, Maddison P. Dietary treatment of rheumatoid cachexia with beta-hydroxy-beta-methylbutyrate, glutamine and arginine: a randomised controlled trial. Clin Nutr 2005;24:442–54.

152 Marcora SM, Lemmey AB, Maddison PJ. Can progressive resistance training reverse cachexia in patients with rheumatoid arthritis? Results of a pilot study. J Rheumatol 2005;32:1031–9.

153 Metsios GS, Stavropoulos-Kalinoglou A, Panoulas VF *et al*. Association of physical inactivity with increased cardiovascular risk in patients with rheumatoid arthritis. Eur J Cardiovasc Prev Rehabil 2009;16:188–94.

154 de Jong Z, Munneke M, Zwinderman AH *et al*. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. Arthritis Rheum 2003;48: 2415–24.

155 Metsios GS, Stavropoulos-Kalinoglou A, Veldhuijzen van Zanten JJ *et al*. Rheumatoid arthritis, cardiovascular disease and physical exercise: a systematic review. Rheumatology 2008;47:239–48.

156 Eknoyan G. Adolphe Quetelet (1796–1874)—the average man and indices of obesity. Nephrol Dial Transplant 2008;23:47–51.

157 Haslam D, Sattar N, Lean M. ABC of obesity. Obesity–time to wake up. Br Med J 2006;333:640–2.

158 Rennie KL, Jebb SA. Prevalence of obesity in Great Britain. Obes Rev 2005;6:11–2.

159 Bray GA. Don't throw the baby out with the bath water. Am J Clin Nutr 2004;79:347–9.