REVIEW

The impact of the metabolic syndrome on cardiovascular risk and disease in rheumatoid arthritis

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The metabolic syndrome is a cluster of cardiovascular risk factors that are of metabolic origin and include atherogenic dyslipidemia, hypertension and hyperglycemia. This syndrome is generally considered to develop as a consequence of excess adiposity-mediated insulin resistance. In rheumatoid arthritis (RA), apart from excess adiposity, high-grade inflammation, routine glucocorticoid use and subclinical hypothyroidism are further implicated in insulin resistance. Several more recently uncovered metabolic risk factors including microalbuminuria, hypercoagulability, autonomic dysfunction, hyperuricemia, renin–angiotensin activation and raised aminotransferase concentrations prior to methotrexate use are also more prevalent in RA subjects as compared with non-RA subjects, linked to other metabolic syndrome components and/or related to RA characteristics. Suppression of RA disease activity improves metabolic cardiovascular risk. Systemic inflammation, glucocorticoid therapy, hypothyroidism, insulin resistance, atherogenic dyslipidemia, hypertension, hypercoagulability, hyperuricemia and raised aminotransferases are each further associated with cardiovascular disease in RA. However, the WHO and the National Cholesterol Education Program defined metabolic syndrome as less strongly associated with atherosclerosis than their components. We propose that individual metabolic risk factors should be considered in the assessment and interventions aimed at reducing cardiovascular risk in this disease. Future prospective investigations need to elucidate molecular mechanisms that account for the interactions between RA characteristics and metabolic risk factors, as well as the relative importance of altering adverse lifestyle factors and intensifying disease activity suppressant therapy in patients with controlled and uncontrolled RA disease activity.

Keywords: cardiometabolic risk, cardiovascular disease, glucocorticoids, high-grade inflammation, hypothyroidism, insulin resistance, metabolic syndrome, obesity, rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease that is complicated not only by progressive articular destruction, but also by increased cardiovascular (CV) event rates [1–7]. In the general population, guidelines on CV risk assessment and the primary and secondary prevention of CV events recommend consideration of the non-modifiable risk factors of age and male gender, and modifiable risk factors of total or low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, blood pressure, smoking habits and diabetes [8]. The Framingham risk equation [9] and the Systemic COronary Risk Evaluation (SCORE) [10], which are calculated from these traditional CV risk factors, are particularly useful in estimating the short-term (10-year) risk for coronary heart disease-related events.

The metabolic syndrome constitutes an additional construct that can enhance our understanding of CV disease, and consists of a group of risk factors that are of metabolic origin and tend to cluster in individuals [11–14]; these risk factors are recognized to be comprised of atherogenic dyslipidemia, high blood glucose concentrations and elevated blood pressure whereas a proinflammatory state and a prothrombotic state were more recently identified as further integral components of the metabolic syndrome [11–14].

A total of 22% of the US population currently has the metabolic syndrome [15], the main determinant of which is excess adiposity that often (but not always) results in insulin resistance, a core pathophysiological mechanism in the metabolic syndrome [11–14]. However, of particular importance in the context of RA, apart from excess adiposity, low-grade systemic inflammation can also induce insulin resistance [16–19]. Therefore, in RA the central feature of high-grade inflammation may enhance atherosclerotic CV disease through the insulin resistance-mediated cluster of CV risk factors [20–22]. For the purpose of this review, we searched PubMed with the terms 'rheumatoid arthritis', 'metabolic syndrome', 'insulin resistance', 'cardiovascular disease', 'coronary heart disease', 'cardiovascular events', 'arterial stiffness', 'endothelial dysfunction', 'high-grade inflammation', 'glucocorticoids' and 'hypothyroidism'. We first discuss the metabolic syndrome as an evolving paradigm in the general

population, with emphasis on aspects that are relevant to its potential application in patients with RA. We subsequently examine how high-grade inflammation and possibly other characteristics (e.g., glucocorticoid therapy) relate to the metabolic syndrome, as well as the potential role of this CV risk factor cluster in atherogenesis and in designing therapeutic strategies that are aimed at preventing CV disease in RA.

The metabolic syndrome in the general population

A paradigm of the metabolic syndrome in the general population is shown in Figure 1.

History

As far back as 1923, Kylin observed that hypertension, hyperglycemia and gout often co-existed in individual patients [23]. Subsequently, central obesity, Type 2 diabetes mellitus (T2DM), lipids and CV disease were also reported to aggregate [24]. In 1988, Reaven coined the term 'syndrome X' in a report in which, based on investigations of the later part of the last century, he proposed that fatty acid-induced insulin resistance and its compensatory hyperinsulinemia could predispose patients to hypertension, dyslipidemia and diabetes, and therefore contribute substantially to CV disease [25]. Thus, a mechanism that could explain the co-occurrence of metabolic risk factors in individual subjects was provided. This cluster of interacting metabolic risk factors was subsequently also referred to as 'the insulin-resistance syndrome' and 'the metabolic syndrome' [14]. Importantly, although Reaven recognized the association of these CV risk factors with obesity, he noted that 25% of nonobese subjects with normal glucose tolerance were also insulin resistant and did not include excess adiposity as a consequence of insulin resistance [14]. Reaven's undertaking drew the attention of many epidemiologists, clinicians and basic scientists. Indeed, several thousands of reported investigations on the metabolic syndrome soon followed [26].

Subsequently, and in order to facilitate the consideration of metabolic syndrome features in the identification of patients with increased CV risk, the WHO published the first set of diagnostic criteria of the metabolic syndrome in 1999 [12]. The WHO defined the metabolic syndrome as the presence of T2DM or impaired fasting glucose/impaired glucose tolerance or insulin resistance, with at least two of the following [12]:

- Hypertension
- Atherogenic dyslipidemia (high triglycerides or low HDL cholesterol)
- Obesity (increased body mass index) or abnormal fat distribution (increased waist-to-hip ratio)
- Microalbuminuria, another CV risk factor that is associated with insulin resistance.

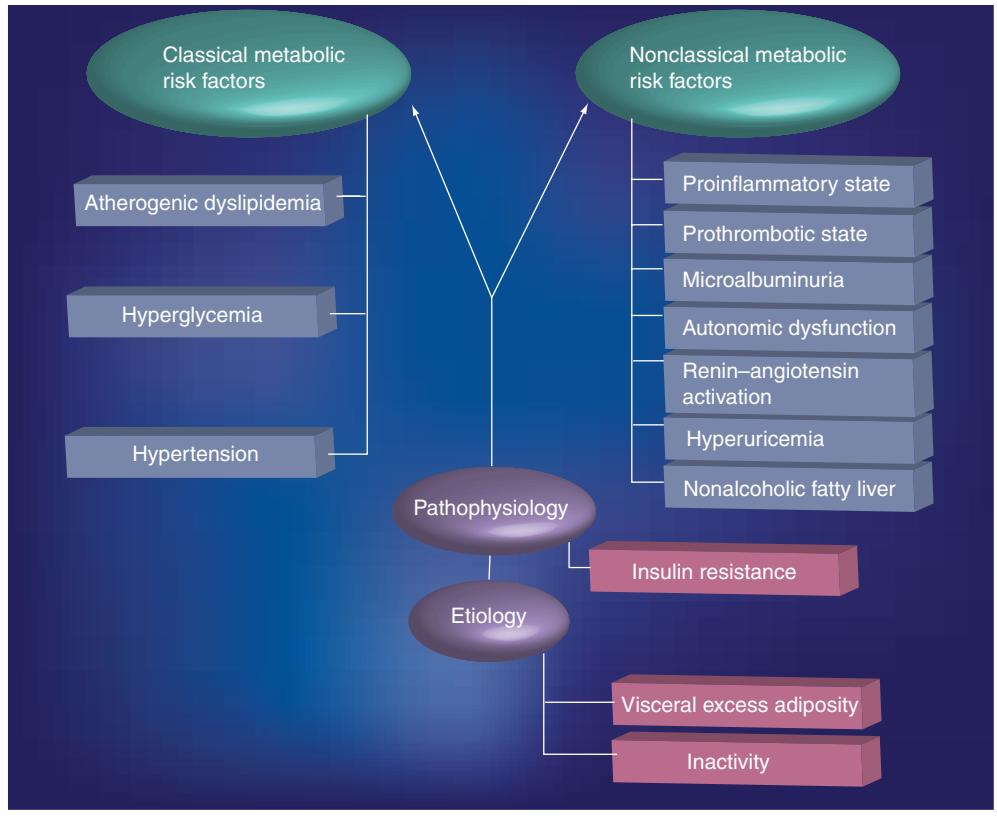
In 2001, due to the increasing rates of obesity, the recognition that obesity is the main determinant of insulin resistance in the general population, and the ease of estimating metabolic syndrome characteristics other than insulin resistance, the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATPIII) [11–14] and, in 2005, the International Diabetes Federation (IDF) [27], defined the metabolic syndrome as the metabolic complications of obesity with the inclusion of the clinical characteristics of abdominal obesity (increased waist circumference), atherogenic dyslipidemia, hypertension and raised fasting plasma glucose concentrations. Thus, a direct measure of impaired insulin sensitivity no longer featured in these definitions. The elucidation of the mechanisms whereby obesity adversely affects traditional and nontraditional metabolic risk factors has the potential to identify new targets in the assessment, prevention and treatment of CV disease [11–14].

In conclusion, in studies on the cluster of metabolic syndrome CV risk factors in non-RA subjects, many investigators have recently altered the focus from insulin resistance to the consequences of excess adiposity.

Pathophysiology

In the general population, the metabolic syndrome is currently considered to develop through an interaction between obesity and metabolic susceptibility that is commonly manifested by insulin resistance [11–14,28]. Mediators of this metabolic susceptibility include physical inactivity, genetic factors, advancing age, endocrine dysfunction and drugs [13,14,28]. Insulin resistance is an impaired biological response to insulin actions in the insulin-responsive organ systems of skeletal muscle, the liver and fat tissues [14,25]. It follows that the well-recognized metabolic consequences of insulin resistance are decreased glucose uptake by fat and muscle tissue and increased hepatic gluconeogenesis that can lead to increased circulating glucose concentrations and compensatory hyperinsulinemia, enhanced free fatty acid release by fat tissue that

Figure 1. Paradigm of the metabolic syndrome in the population at large.



can result in increased triglycerides and reduced HDL cholesterol concentrations, and protein catabolism [25,29]. Since atherogenesis is now known to be an inflammatory process [30], it is particularly relevant that apart from the effects of insulin on carbohydrate, fat and protein metabolism, more recently identified biological actions of insulin comprise of anti-inflammatory effects through decreasing nuclear factor κB and increasing inhibitor of κB, reducing reactive oxygen species, circulating adhesion molecules and monocyte chemoattractant protein-1, in addition to profibrinolytic actions by decreasing plasminogen activator inhibitor-1 production [31]. Resistance to insulin could therefore accelerate atherogenesis not only through the development of classical metabolic risk factors, but also by directly generating a proinflammatory and prothrombotic state, which are newly recognized components of the metabolic syndrome.

Assuming that obesity is the most prevalent etiological factor, and that insulin resistance is the core pathogenetic mechanism in the development of metabolic CV risk factors, the question arises as to how excess fat tissue interacts with insulin sensitivity at a molecular level. Abdominal obesity is characterized by enlarged fat cells, as well as increased numbers of monocyte-derived macrophages within the adipose tissue [14,32]. These enlarged adipocytes release an excess of free fatty acid that impairs the actions of insulin in muscle and liver tissues [14,32]. Enlarged fat cells and their surrounding macrophages further produce an excess of adipokines, including leptin and resistin and decreased quantities of adiponectin, together with increased amounts of the adipocytokines tumor necrosis factor-α (TNF-α) and interleukin (IL)-6, each of which, in addition to free fatty acid, contribute to impaired insulin sensitivity [14,32].

In conclusion, in non-RA subjects, clustering of the metabolic syndrome CV risk factors originates in excess visceral adiposity-derived free fatty acids, adipokines and cytokines that result in insulin resistance, which mediates atherogenic dyslipidemia, hypertension, hyperglycemia and a proinflammatory and prothrombotic state.

Clinical utility

A recent meta-analysis of longitudinal studies revealed that the metabolic syndrome was associated with a relative risk of CV events and

death of 1.54 (95% CI: 1.32–1.79) after adjustment for traditional CV risk factors [33]. The metabolic syndrome is also associated with a fivefold increased risk for the development of T2DM [11–14]. However, the metabolic syndrome is an evolving construct. Two recent papers, one by Reaven [33] and the other by Kahn and colleagues on behalf of the American Diabetes Association and European Association for the Study of Diabetes [26], have recently questioned the clinical utility of the metabolic syndrome in the assessment of CV risk. Questions that currently surround the metabolic syndrome and their potential answers are shown in Table 1.

As mentioned previously, apart from obesity, other etiological factors such as inactivity and drugs are involved in the development of metabolic syndrome [13,32] and, apart from insulin resistance, low-grade systemic inflammation [16–19] has been strongly implicated in the pathophysiology of the metabolic syndrome. Indeed, inactivity is associated with insulin resistance [14] and elevated levels of the proinflammatory marker high-sensitivity C-reactive protein (hs-CRP), which is associated with many other metabolic syndrome features [34]. Moreover, apart from causing obesity, the excessive intake of carbohydrates and saturated fats were recently also shown to directly induce several proinflammatory effects, including the increased production of reactive oxygen species, upregulation of nuclear factor κB in monocytes and polymorphonuclear cells and CRP production [31].

Since insulin resistance and systemic inflammation further predict CV disease independent of the current WHO and NCEP-ATPIII-defined metabolic syndrome [19,35,36], the inclusion of these easily assessable pathophysiological characteristics in metabolic syndrome definitions has the potential to further improve CV assessment. Furthermore, other more recently identified CV risk factors that cluster with the classical metabolic syndrome features include, apart from inflammation and the previously mentioned microalbuminuria and prothrombotic state, autonomic dysfunction, hyperuricemia, renin–angiotensin activation and nonalcoholic fatty liver disease [11–14]. Since all the CV risk owing to the metabolic syndrome is not captured by currently recommended definitions, the role of the inclusion of these metabolic risk factors in future definitions for CV risk assessment also requires further investigation.

The optimal threshold values of metabolic risk factors for inclusion as defining criteria requires further investigation, an undertaking that may be complicated by the 'dose–response' effect of these risk factors of CV disease.

Although CV risk factors typically act multiplicatively in atherogenesis, recent evidence indicates that CV disease associated with the NCEP-ATPIII defined metabolic syndrome is not greater than that associated with the sum of its parts [37]. Very recently, Sattar and colleagues [38] investigated to what extent the metabolic syndrome and its individual components were related to the risk of events of incident CV disease and T2DM in 7549 nondiabetic subjects aged 60–82 years. The metabolic syndrome predicted incident diabetes, but not to a greater extent than impaired fasting glucose, and was weakly or not associated with vascular risk in these elderly subjects [38]. This study strongly argues against the use of the metabolic syndrome concept as a tool to assess the risk for CV disease. The respective findings further support the notion that current metabolic syndrome definitions may require optimization.

The NCEP-ATPIII metabolic syndrome definition does not perform as well as the Framingham score in predicting short-term (10-year) CV disease in the general population. This is not unexpected, since potent non-metabolic risk factors such as age and smoking are not included in metabolic syndrome definitions. Indeed, the metabolic syndrome was not introduced to replace previously designed and comprehensive CV risk engines, but rather as an additional and supplemental tool to enhance CV risk assessment and the prevention of CV disease by addressing lifestyle factors that complicate urbanization [13,28,32]. The extent to which inclusion of the several more recently recognized components of the metabolic syndrome in metabolic syndrome definitions could result in more effective CV disease and T2DM risk prediction requires further investigation.

With regard to the therapeutic implications of the presence of metabolic syndrome, the dramatically increasing prevalence of the etiological factors of excess adiposity and its frequently co-existent inactivity, and the resulting development of metabolic risk factors in the population at large, substantiate the need for formal CV risk assessment, addressing lifestyle factors and targeting drug therapy towards ameliorating the different metabolic syndrome risk factors, as well as the underlying mechanisms such as insulin resistance [11–14,28].

Table 1. Questions and their potential answers that currently surround the metabolic syndrome construct.

Question	Answer
Does the metabolic syndrome have a clear-cut etiopathogenesis?	Many etiological factors (e.g., obesity, inactivity and drugs) and pathophysiological mechanisms (e.g., insulin resistance and inflammation) may be involved
Which metabolic syndrome features should be included in metabolic syndrome definitions?	Insulin resistance and inflammation predict cardiovascular disease over and above the current metabolic syndrome criteria and these risk factors as well as other more recently identified metabolic syndrome components may need to be included
What are the optimal threshold values for each of the metabolic syndrome criteria?	Current threshold values may be too arbitrary and the relationship between these metabolic risk factors and cardiovascular disease may be of a continuous nature
Is the cardiovascular risk that is associated with the syndrome greater than the sum of its parts?	A recent study revealed that the current National Cholesterol Education Program's Adult Treatment Panel III definition was no longer associated with cardiovascular disease once the individual criteria were adjusted for. In a recent large prospective study the metabolic syndrome was associated with incident Type 2 diabetes, but not or weakly with cardiovascular risk
Does the metabolic syndrome perform as well as other cardiovascular risk engines in predicting cardiovascular disease?	The Framingham score performs better than the metabolic syndrome in predicting cardiovascular disease but the aim of the metabolic syndrome construct is to supplement rather than replace other cardiovascular risk scores
What are the current therapeutic implications of diagnosing the metabolic syndrome?	A diagnosis of the metabolic syndrome calls for formal cardiovascular risk assessment and addressing lifestyle factors
What are the future therapeutic implications of diagnosing the metabolic syndrome?	A diagnosis of the metabolic syndrome may call for the use of a 'poly pill' combining several agents that improve different metabolic risk factors and the development of agents that influence core pathophysiological mechanisms

Current metabolic syndrome definitions for CV risk assessment in the general population are likely to need optimization in the years to come. In RA, the interaction of disease-specific factors with metabolic syndrome features may further complicate the application of these definitions in CV risk assessment.

In conclusion, in non-RA subjects, the identification of the metabolic syndrome should reinforce the need to address lifestyle factor alterations in CV disease risk reduction. However, other risk engines, such as the Framingham equation [9] and the SCORE function [10], rather than current metabolic syndrome definitions, should be used to assess CV risk in the clinic.

The metabolic syndrome in RA

Studies that were performed in patients with RA and that included comprehensive CV risk assessment, together with the evaluation of the presence of subclinical or established CV disease, have consistently revealed that, in addition to classical CV risk factors as routinely recommended in CV risk estimation in non-RA subjects, several nontraditional CV risk factors contribute to atherogenesis [39–42]. Since the metabolic syndrome comprises a cluster of relatively recently uncovered and interacting risk factors that include systemic inflammation, and since its presence has implications in the assessment and prevention of CV disease, elucidation of the role of this construct in RA atherogenesis is particularly pertinent at this point in time. Even more importantly, reported findings on the influence of inflammation on metabolic risk factors in non-RA subjects may not apply to the RA population, since the latter experience a much higher inflammatory burden as compared with those seen in the population at large [20–22].

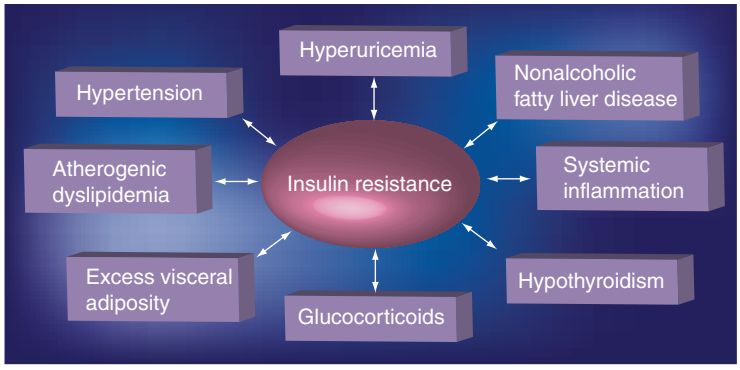
Interactions between RA characteristics & metabolic syndrome features in RA

Metabolic risk factors that are associated with insulin resistance in RA are shown in Figure 2.

Adiposity in RA

In patients with RA, most investigators have not found an increased prevalence of excessive generalized adiposity as assessed by the body mass index (BMI). However, both we [43] and Chung and colleagues [44] previously found an increased

Figure 2. Metabolic risk factors that are associated with insulin resistance in rheumatoid arthritis.



central adiposity as assessed by waist circumference measurements in the presence of similar BMIs in RA patients as compared with non-RA subjects. The importance of this finding lies in the fact that abdominal obesity is more strongly associated with cardiometabolic risk than generalized obesity [11–14,27]. Furthermore, using bioelectrical impedance, Stavropoulos-Kalinoglou *et al*. [45] recently demonstrated that patients with RA experience a BMI that is reduced by 1.83 kg/m^2 for a given body fat mass, indicating that a BMI of over 23 kg/m^2 and over 28 kg/m^2 (as opposed to over 25 and 30 or more in the general population) should be considered as reflecting overweight and obesity, respectively, in this disease. This observation is in line with the entity of 'rheumatoid cachectic obesity' that was previously reported by Rall and Roubenoff [46]. This complication of RA results from the loss of body cell mass, consisting mainly of a reduced muscle mass in the presence of stable weight and increased fat mass, and affects nearly two-thirds of RA patients [46]. These changes are related to enhanced protein catabolism induced by increased circulating cytokine concentrations, the use of glucocorticoids, physical inactivity and, possibly, hormonal alterations that include reductions in growth hormone and insulin like growth factor-1 and high-grade inflammation-induced insulin resistance [43,46,47].

Obesity influences disease outcome characteristics in patients with RA (that determine CV and overall mortality) in that its presence is independently associated with reduced radiographic progression [48,49], impaired/poorer quality of life [50] and a reduced response to classical disease-modifying agent therapy [51] in RA. The adverse effects of obesity on metabolic risk factors including insulin resistance, hypertension, atherogenic dyslipidemia and systemic inflammation translate to increased coronary heart disease and mortality rates in the population at large [52–54]. However, in 2004, Maradit-Kremers *et al*. [55] found that RA patients with a low BMI (waist circumference was not reported on) experienced a higher incidence of CV mortality as compared with those with a normal or high BMI, even after adjusting for age, gender, personal cardiac history, smoking status and the presence of diabetes, hypertension and malignancy [55]. Notably, since disease activity and severity that are reportedly associated with altered adiposity in RA were not adjusted for, further study on the impact of decreased adiposity on CV risk in RA is needed. In line with the findings of Maradit-Kremers in 2005, Escalante *et al*. [56] reported an inverse association between BMI and overall mortality in RA. Of particular relevance in the present context, these investigators further showed that this relationship was explained by comorbidities and disease severity in multivariable regression models [56]. In addition, the protective effect of a high BMI occurred only if the erythrocyte sedimentation rate was low [56]. Further investigations in which CV risk is compared between RA subjects with similar disease activity, but with or without central obesity, may need to be performed in order to determine whether the relationship between excess adiposity and CV risk differs or even contrasts between RA subjects as compared with non-RA subjects.

Insulin resistance, atherogenic dyslipidemia & hypertension in RA

The notions that insulin resistance is the most established pathophysiological mechanism in the metabolic syndrome, and low-grade inflammation and glucocorticoids can induce insulin resistance in non-RA subjects, prompted us to investigate the potential roles of high-grade inflammation and glucocorticoid therapy as used in RA, in impaired insulin sensitivity in this disease. We further assessed the association of insulin resistance with atherogenic dyslipidemia, another major risk factor component of the metabolic syndrome. In keeping with previously reported studies in which glucose loading was used to assess insulin sensitivity [57–59], we found an increased prevalence of insulin resistance as assessed by the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and the Quantitative Insulin Sensitivity Check Index (QUICKI) in patients with inflammatory arthritis (RA, spondyloarthropathy and undifferentiated inflammatory arthritis) as compared with

healthy controls [60]. Upon using acute-phase responses as surrogate markers of systemic inflammation, a consistent association with insulin resistance was revealed in inflammatory arthritis [60,61]. Moreover, impaired insulin sensitivity was significantly associated with both low HDL cholesterol and high triglycerides [61], abnormalities that are recognized to reflect the lipid component of atherogenic dyslipidemia in RA, whereas such a relationship was not present in age-, gender- and race-matched control subjects with osteoarthritis [61]. We then confirmed these cross-sectional data in a longitudinal study in which we re-assessed cardiovascular risk factors 2–3 months subsequent to the initiation of DMARDs in combination with pulsed glucocorticoids that were employed only at the outset and as bridge therapy to accelerate the DMARD response [62]. This intervention resulted in enhanced insulin sensitivity and a reduction in atherogenic dyslipidemia. Improved blood glucose and blood pressure control in patients with diabetes and hypertension, respectively, was also observed, although the small number of patients with these metabolic risk factors precluded confirmation by statistical analysis [62]. Thus, high-grade systemic inflammation in RA clearly clusters with insulin resistance, and its suppression is associated with an improvement in this core pathophysiological mechanism in the metabolic syndrome, as well as in each of its most recognized consequent CV risk components. Suppression of RA disease activity is known to result in increased cholesterol burden as assessed by total or LDL cholesterol as well as HDL cholesterol concentrations, thereby leaving the atherogenic index (total cholesterol/HDL cholesterol) unaltered [20]. In this regard, we noted that dietary intervention aimed at reducing excess weight and its linked metabolic risk factors resulted in a decrease in cholesterol burden, as opposed to the expected increase [62]. Although dietary intervention did not alter insulin sensitivity overall, it induced a reduction in weight that was associated with an increase in insulin sensitivity [62]. These data support the adjunctive use of dietary intervention in reducing cardiometabolic risk in RA. Subsequent to the above-mentioned investigation, RA disease activity suppression with the TNF-α antagonist infliximab [63–65], but not adalimumab [66], was shown to be associated with enhanced insulin sensitivity as well as increases in the different circulating lipid concentrations and in the absence of alterations in cholesterol to HDL cholesterol ratios.

Glucocorticoids have long been documented to adversely affect glucose metabolism with the development of insulin resistance, as well as that of T2DM. An association between glucocorticoid therapy and the incidence of diabetes was reported in RA [67]. In a separate investigation, we found that previous oral glucocorticoid exposure and the use of high doses of pulsed glucocorticoids were associated with insulin resistance independent of adiposity, but not with other metabolic syndrome features including obesity, hypertension and dyslipidemia [68]. In fact, other investigators have shown that glucocorticoid therapy is associated with increased HDL cholesterol concentrations [69]. On the other hand, with regard to hypertension, in a more recent investigation by Panoulas *et al.* [70] in patients with RA who were older and in whom oral prednisone was used more frequently and at higher doses as compared with in participants in our studies, the use of prednisone at doses of 7.5 mg or over daily was independently associated with hypertension.

Another potential contributor to insulin resistance is subclinical hypothyroidism, an endocrine disorder in which circulating thyroxine concentrations are normal in the presence of raised circulating thyrotropin concentrations [71]. Indeed, subclinical hypothyroidism is associated with the metabolic syndrome components of hypertension, raised triglyceride and low HDL cholesterol concentrations and elevated cholesterol:HDL cholesterol ratios [71]. We found that subclinical hypothyroidism that was mostly associated with increased circulating concentrations of thyroid antibodies was present in 11% of 126 patients with RA and, in multivariable analysis, this endocrine disorder predicted insulin resistance independently of adiposity, physical activity, smoking, alcohol consumption, systemic inflammation and glucocorticoid therapy [71]. Molecular mechanisms underlying these potential interactions await identification.

If RA characteristics and, in particular, high-grade systemic inflammation mediate impaired insulin sensitivity, and a high BMI protects against CV disease in RA, the question arises as to whether excess weight (the main determinant of insulin resistance in non-RA subjects) has any impact on insulin sensitivity in RA and, therefore, should be considered in the assessment of cardiometabolic risk in this disease. We therefore evaluated the relative impact of adiposity and other non-RA characteristics versus disease-specific features on impaired insulin sensitivity [47]. Associations of these different factors with impaired β-cell

function (HOMA-B), an essential pathogenetic mechanism in the development of T2DM, were also investigated [47]. This study revealed that central adiposity as assessed by waist circumference was more strongly related to insulin resistance than disease activity. Age and disease activity were associated with reduced β-cell function, whereas cumulative glucocorticoid doses and angiotensin converting enzyme inhibitors and angiotensin receptor blockers that were used to treat hypertension, were associated with enhanced β-cell function. With a mean disease duration of 5.8 years, the cumulative glucocorticoid dose was as low as 0.5 g. Our findings indicate that the sparing use of glucocorticoid with tailoring towards disease activity, as was applied in this cohort, may improve β-cell function through anti-inflammatory effects that outweigh their known adverse effects on glucose metabolism. The previously reported negative association between excessive generalized adiposity and CV disease [55] and overall mortality [56] seemingly contrast with our findings of an adverse effect of central obesity on glucose metabolism. These apparently discrepant results can, we believe, illustrate an effect of the current trend towards tighter disease activity control and its expected consequent reduced disease severity, as applied to our patients. Indeed, tighter control of high-grade systemic inflammation would be expected to attenuate its effects on metabolic risk factors in a disease like RA. This could thereby result in a chain of events in the development of metabolic syndrome features that is more similar to that seen in non-RA subjects, and in which central obesity is now also playing a major role in impaired insulin sensitivity in RA. The relationship between excess adiposity and CV disease may therefore need to be readdressed in the current era of tight disease activity control. However, this study was cross-sectionally designed and circulating cytokines that more directly reflect systemic inflammation in RA were not evaluated.

In conclusion, in RA subjects, apart from excess adiposity, several RA characteristics, including high-grade inflammation, glucocorticoid therapy and hypothyroidism, may further contribute to insulin resistance and its associated CV risk factors.

Nonclassical metabolic syndrome components in RA

In non-RA subjects, low-grade systemic inflammation that has been mostly estimated by circulating hs-CRP concentrations is mainly determined by visceral adiposity [20]. Other factors that contribute include age, male gender, smoking, chronic infections and estrogen use [72]. Mutually reinforcing interactions between metabolic risk factors are characteristic in the metabolic syndrome, and this includes the relationship between insulin resistance and inflammation [72]. However, in RA, systemic inflammation as reflected by elevated CRP concentrations is generally considered to result from the effect of inflamed joint-derived IL-6 on the liver. We found that 44% of 94 RA patients had central obesity as determined by the presence of an increased NCEP-ATPIII defined waist circumference and, interestingly, in these patients, the HOMA-IR explained as much of the variability of hs-CRP concentrations as did disease activity (disease activity score 28) [72]. Furthermore, smoking was also independently associated with systemic inflammation in these patients [72]. These findings suggest that, in addition to RA disease activity, non-RA characteristics and, in particular, insulin resistance in patients with central obesity, should be considered when evaluating the impact of systemic inflammation on CV disease in RA.

Apart from systemic inflammation, several other nonclassical risk factors that are now known to cluster with the most established metabolic syndrome components as incorporated in the NCEP-ATPIII metabolic syndrome, have been reported on in RA (Box 1). Pedersen *et al.* [73] documented an increased urinary albumin:creatinine ratios in 27.7% of 65 patients with RA; microalbuminuria was further associated with CRP concentrations. McEntegart *et al.* [74] reported significant elevations of the procoagulant factors of fibrinogen, von Willebrand Factor and tissue plasminogen antigen and fibrin D-dimer concentrations, but not of PAI-1 concentrations, and suggested that these molecules may contribute to the excess CV disease as experienced by patients with RA. Several studies revealed the presence of autonomic dysfunction with an increased sympathetic nervous system tonus that may result from decreased hypothalamic–pituitary–adrenal axis activity and can be reduced by TNF-α blockade [75]. Uric acid concentrations are not increased in patients with RA. However, Panoulas *et al.* [76,77] recently demonstrated a relationship of uric acid concentrations with insulin resistance, as well as hypertension and atherogenic dyslipidemia in RA. Hyperuricemia is now a documented modifiable risk factor for hypertension and CV disease in non-RA subjects [78]. Boers *et al.* [79] reported increased circulating renin and prorenin in RA patients with vasculitis as compared with those without this

Box 1. Cardiovascular risk factors that are associated with both insulin resistance and cardiovascular disease in rheumatoid arthritis.

Etiological factors in the metabolic syndrome

- Systemic inflammation
- Glucocorticoids
- Hypothyroidism

Pathophysiological mechanism of the metabolic syndrome

- Insulin resistance

Metabolic risk factors of the metabolic syndrome

- Hypertension
- Atherogenic dyslipidemia
- Type 2 diabetes mellitus
- Prothrombotic state
- Hyperuricemia
- High aminotransferase concentrations

extra-articular manifestation. Finally, we recently found that in patients with RA who are investigated prior to taking methotrexate, serum aminotransferase concentrations were associated with insulin resistance independent of age, gender and adiposity; RA characteristics were not associated with aminotransferase concentrations [80]. Elevated aminotransferases are surrogate markers of liver fat content, whereas nonalcoholic fatty liver disease contributes to insulin resistance independent of visceral adiposity, and thereby constitutes a novel etiopathogenetic mechanism in the metabolic syndrome [80]. Future RA studies in which liver fat content is directly measured are warranted.

Although a systematic review of reports on adipokine metabolism in RA is beyond the scope of this review, importantly adiponectin was found to be produced by human synovial fibroblast in this disease, and to enhance articular inflammation and matrix degeneration [81]. Adiponectin, the production of which is reduced in subjects with visceral obesity, has both insulin-sensitizing and anti-inflammatory effects [14]. The findings by Ehling *et al*. indicate that inhibition of the production or biological effects of adiponectin may comprise a potential therapeutic strategy in RA [81]. However, whereas both increased and unaltered circulating adiponectin concentrations were reported in this disease, we recently found that low circulating adiponectin concentrations were associated with atherogenic dyslipidemia and high fasting plasma glucose concentrations as applies to non-RA subjects [82]. Thus, prior to the use of specific adiponectin inhibition, the biological effects of circulating adiponectin on the vascular system in RA are required. Furthermore, selective intra-articular inhibition that does not affect the biological effects of circulating adiponectin may need to be considered. Interestingly, we also found that circulating adiponectin concentrations were inversely related to systemic inflammation as assessed by CRP concentrations, but not to the BMI or insulin sensitivity [82]. It follows that high-grade inflammation could result in decreased circulating adiponectin concentrations in RA. Indeed, RA disease activity suppression with TNF-α blockade consisting of infliximab and etanercept [83] (but not adalimumab [84]) was now reported to increase circulating adiponectin concentrations. Taken together, whereas intra-articularly produced adiponectin is proinflammatory in RA, joint-derived high-grade systemic inflammation may reduce the release of adiponectin, probably by visceral adipocytes [85], in the circulation, and this may contribute to the enhanced CV event rates experienced by patients with RA.

In conclusion, several nontraditional metabolic syndrome components may be more prevalent in RA subjects as compared with non-RA subjects, linked to other metabolic syndrome features and/or RA characteristics. The relative impact of insulin resistance versus disease characteristics on microalbuminuria, the prothrombotic state, autonomic dysfunction and renin–angiotensin activation requires further study in RA.

Metabolic syndrome components, current metabolic syndrome definitions & CV disease in RA

As previously discussed, the previously reported inverse relationship between general adiposity and CV event rates and mortality in RA may need to be readdressed in the current era of tight disease activity control. Furthermore, we [86] and others [44] did not find a relationship between visceral adiposity and ultrasonographically determined carotid artery and electron beam computed tomography-detected coronary artery atherosclerosis, respectively, in patients with RA. However, it is of interest that, in RA, the potential determinants of insulin resistance other than adiposity were each shown to be independently associated with CV disease. Indeed, an association between systemic inflammation and CV disease has now been amply documented in RA [39–41,87,88] and, as previously discussed, this relationship could be determined not only by RA disease activity, but also by insulin resistance and smoking [72]. In RA, glucocorticoid use is associated with atherosclerosis [89]. Finally, hypothyroidism is not only independently associated

with ultrasonographically determined carotid artery atherosclerosis [39], but also with a fourfold increase risk of coronary, cerebral or peripheral artery arterial disease in female RA patients [90].

With regard to the core mechanism of insulin resistance and conventional components of the metabolic syndrome, again each of these is associated with CV disease in RA. Indeed, insulin resistance, hypertension, atherogenic dyslipidemia and T2DM are each independently associated with the presence of both carotid and coronary artery atherosclerosis [39,40,44,86]. Additionally, the nontraditional procoagulant factors PAI-1 and TPA predict CV event rates [91], serum uric acid concentrations are associated with carotid atherosclerosis [39], and CV events rates [76] and raised serum aminotransferase concentrations prior to methotrexate use are associated with carotid atherosclerosis [80] in RA.

The consistent associations of the different metabolic syndrome components with CV disease certainly support the notion that these risk factors may be valuable in the assessment and prevention of CV disease in RA. However, the controversy surrounding the application of currently recommended metabolic syndrome definitions in non-RA subjects and the potential contribution of several disease-specific characteristics to the metabolic syndrome features in RA, indicate a need to address the clinical utility of the respective definitions in determining CV risk in this chronic inflammatory disorder. We have previously shown that, although the NCEP-ATPIII metabolic syndrome has a specificity of 100%, its sensitivity is as low as 23% in detecting the key metabolic syndrome mechanism of insulin resistance in RA [92]. Subsequently, we assessed the association of the NCEP-ATPIII metabolic syndrome and the WHO metabolic syndrome with carotid artery intima-media thickness and plaque [86]. In multivariable regression analysis, the NCEP metabolic syndrome was not associated with atherosclerosis. The WHO metabolic syndrome was associated with carotid artery plaque, but not with intima-media thickness. In contrast to these currently recommended metabolic syndrome definitions, the individual metabolic syndrome components of hypertension, insulin resistance and high triglycerides were each independently associated with both carotid artery intima-media thickness and plaque [86]. At approximately the same time, Chung and colleagues [44] published their findings on the association of the NCEP-ATPIII metabolic syndrome and the WHO metabolic syndrome with coronary artery atherosclerosis. As compared with in our cohort, the NCEP-ATPIII metabolic syndrome and the WHO metabolic syndrome were found approximately twice as frequently. This is not surprising since the BMI was 3–4 kg/m^2 higher and prednisone was used approximately five-times as often in the patients of Chung and colleagues as compared with in our cohort [44]. Despite these differences in baseline recorded variables, their main findings were remarkably similar to ours: the NCEP-ATPIII metabolic syndrome and the WHO metabolic syndrome were not associated with coronary artery calcification scores once previously identified CV risk factors in RA were controlled for. By contrast, hypertension, insulin resistance and dyslipidemia were independently associated with coronary artery atherosclerosis. The association of insulin resistance with ultrasonographically determined carotid artery atherosclerosis was confirmed in two further studies [93,94].

Chung *et al*. [44] and Karvounaris *et al*. [95] compared the prevalence of the metabolic syndrome in patients with RA to that in control subjects. In the Chung study, both the NCEP-ATPIII and the WHO-defined metabolic syndrome were more prevalent in RA patients. By contrast, in the Karvounaris study, the prevalence of the NCEP-ATPIII-defined metabolic syndrome was not increased in RA. However, this discrepancy may be owing to the fact that in the Karvounaris study, the waist circumference was atypically higher in controls than in RA subjects. Also, the WHO metabolic syndrome and insulin sensitivity were not reported on in the Karvounaris study [95]. In keeping with our previously reported findings on the interaction between inflammation and insulin resistance in RA [60–62], Karvounaris and colleagues [95] demonstrated a correlation between RA disease activity and the metabolic syndrome, thereby further substantiating the paradigm in which RA characteristics may enhance the risk for atherosclerotic CV disease through their adverse effects on metabolic syndrome components.

Taken together, optimal CV risk reduction in RA is likely to comprise consideration of the impact of the components of currently recommended metabolic syndrome definitions, as well as of the more recently uncovered components in non-RA subjects and several CV risk factors that are RA characteristics.

Conclusion

The metabolic syndrome comprises of a cluster of multiple intricately interacting CV risk factors that are of metabolic origin. In the population at large,

identifying metabolic syndrome features translates into considering the effects mainly of the increasingly prevalent excess adiposity and often concurrent inactivity on CV risk, as well as the necessity to perform a formal CV risk assessment and address adverse lifestyle factors and adjust drug therapy in CV disease prevention. In patients with RA, disease-specific characteristics, particularly high-grade inflammation, further aggravate metabolic syndrome features that, as in non-RA subjects, are associated with CV disease. We therefore propose that metabolic syndrome features should be addressed when assessing CV risk and designing strategies aimed at preventing CV disease in RA. So far, reported evidence indicates that cardiometabolic risk assessment in RA should focus on the individual metabolic syndrome components rather than on determining whether patients meet the metabolic syndrome criteria as currently defined by the WHO and the NCEP-ATPIII.

Future perspective

Current metabolic syndrome definitions for application in CV risk assessment in the population at large are likely to be optimized, mostly through the incorporation of the more recently uncovered integral components of the metabolic syndrome, in the years to come. Whether these updated metabolic syndrome definitions will be appropriate for application in patients with RA will need further investigation. Alternatively, RA-specific metabolic syndrome definitions may be required, and these may further have the potential for application in other chronic high-grade inflammatory disorders. Much of the thus far reported data on metabolic syndrome features in RA are derived from cross-sectional studies and need confirmation in longitudinal observational and interventional studies. The molecular mechanisms that account for the interaction between RA characteristics and meta-

Executive summary

- The metabolic syndrome is a cluster of cardiovascular (CV) risk factors that are of metabolic origin.

The metabolic syndrome in the general population

- History: obesity is increasingly recognized as the main etiological factor in the metabolic syndrome.
- Pathophysiology: resistance to insulin results in adverse fat, carbohydrate and protein metabolism, as well as a proinflammatory and prothrombotic state. Excess visceral fat mediates insulin resistance through the aberrant release of free fatty acids, adipokines and adipocytokines.
- Clinical utility: the consideration of the metabolic syndrome enhances CV risk assessment and reduction through addressing adverse lifestyle factors and adjusting drug therapy.

The metabolic syndrome in rheumatoid arthritis – interactions between rheumatoid arthritis characteristics & metabolic syndrome features

- Adiposity in rheumatoid arthritis (RA): RA patients experience high-grade inflammation-induced reduction in muscle mass together with excess fat accumulation. Generalized adiposity is, however, reportedly inversely associated with CV and overall mortality in RA.
- Insulin resistance, atherogenic dyslipidemia and hypertension in RA: high-grade inflammation, routine glucocorticoid therapy and subclinical hypothyroidism contribute to insulin resistance in RA. Central obesity is also strongly associated with insulin resistance in RA. The sparing use of glucocorticoid therapy tailored towards disease activity may enhance β-cell function.
- Nonclassical metabolic syndrome components in RA: apart from RA disease activity, metabolic syndrome features and smoking further contribute to high-sensitivity C-reactive protein concentrations in RA. The metabolic syndrome components of microalbuminuria, hypercoagulability, autonomic dysfunction, hyperuricemia, renin–angiotensin system activation, nonalcoholic fatty liver disease and altered adiponectin production are more prevalent, linked to other metabolic syndrome components and/or related to RA characteristics.
- In RA, systemic inflammation, glucocorticoid use and hypothyroidism, which are potential determinants of insulin resistance, are also associated with CV disease.
- Insulin resistance, hypertension, atherogenic dyslipidemia, hypercoagulability, hyperuricemia and raised aminotransferases prior to methotrexate use are associated with CV disease in RA.
- Individual metabolic syndrome components are more strongly associated with CV disease than the current National Cholesterol Education Program's Adult Treatment Panel III and WHO metabolic syndrome definitions.

Future perspective

- How to assess cardiometabolic risk in RA as compared with non-RA subjects requires further study.
- The molecular mechanisms that account for the interaction between high-grade inflammation and metabolic syndrome features should contribute to effective drug therapy discovery and development.
- More aggressive disease activity suppression in patients with persistently active RA and improving adverse lifestyle factors in patients with controlled disease are expected to constitute cornerstones of cardiometabolic risk reduction in RA.

bolic syndrome features need elucidation and may provide pivotal information for effective drug discovery and development. Last but not least, optimal interventions aimed at reducing cardiometabolic risk in patients with tightly controlled disease is likely to differ from that in patients with persistent high disease activity. In the former, addressing adverse lifestyle factors would be expected to be most important, as applies to non-RA subjects. In the latter, intensification of disease activity suppressant therapy may constitute the cornerstone. Future studies that address these issues have the potential to assist us in the curtailment of the excess in CV disease burden as currently experienced by patients with RA.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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