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Adipokines in rheumatoid arthritis

Elis Carolina de Souza Fatel[1,5*], Flávia Troncon Rosa[2], Andréa Name Colado Simão[3] and Isaias Dichi[4]

Abstract

Rheumatoid arthritis affects millions of people worldwide and is considered a chronic multisystem disease whose causes are unknown. In general, the main objective of rheumatoid arthritis treatment is to improve the quality of life of patients by relieving pain, maintaining or improving functional capacity, preventing thus, disability. In recent years the role of adipokines in the pathogenesis of rheumatoid arthritis has been discussed but results are still conflicting. Although results from some studies have shown the implications of adipokines in the pathophysiology of autoimmune diseases, including rheumatoid arthritis, their role in the pathogenesis of disease progression is not clear. Thus, this review aimed to describe the association of key adipokines (leptin, resistin, visfatin and adiponectin) and rheumatoid arthritis, given the high prevalence of this disease and the important social impact caused by this chronic disabling disease.

Keywords: Adipokines, Rheumatoid arthritis, Cytokines

Background

Rheumatoid arthritis (RA) is a chronic multisystem disease whose causes are unknown [1]. This disease presents a variety of systemic manifestations being the persistent inflammatory synovitis the most typical feature, compromising peripheral joints in a symmetric distribution. Mateen et al. (2016) [2] highlights RA as a disease, which is characterized in the majority of patients by the presence of rheumatoid factor (RF) and anti–citrullinated protein antibody (ACPA). The authors reinforce that cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-17 have an important role in the pathophysiology of RA since serum concentrations of these substances may indicate the severity of the disease.

The diagnosis of RA must be at earlier stages of disease and treatment should aim to relieve pain, maintain or improve functional capacity, preventing thus, disability, and improving patients quality of life [3].

Barbosa et al. (2012) [4] reported the important role of mediators synthesized in adipose tissue, named adipokines, in RA. Hutcheson (2015) [5] points out that knowledge about adiposity has changed and currently it appears as an important regulator of several key processes, including inflammation. Furthermore, adipokines have hormonal action supporting the regulation of appetite and glucose metabolism, and some of them such as leptin, resistin, adiponectin and visfatin have been associated to RA development. However the results are still conflicting [4, 5].

Thus, this review aimed to describe the association of key adipokines (leptin, resistin, visfatin and adiponectin) and RA, given the high prevalence of this disease and the important social impact caused by chronic disabling diseases of the articular system.

Methods

Study selection

This review is in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [6]. The search string was restricted to humans, including clinical studies, controlled clinical trials, meta-analysis, multicentric, observational studies, and randomized controlled trials. Relevant articles that were not retrieved in the main search but were cited in the publications were carefully reviewed and included if they met the criteria. As the main objective was to verify the association of adipokines with rheumatoid arthritis, most of the studies analyzed refer to observational studies such as cross-sectional, case-control and cohort studies presenting quantitative information regarding plasma or serum adipokines concentrations. The on line databases U.S. National Library of Medicine PUBMED, Periódicos

* Correspondence: elis.fatel@uffs.edu.br; elis.fatel@hotmail.com
[1]Postgraduate Program, Health Sciences Center, State University of Londrina, Londrina, Paraná, Brazil
[5]Department of Nutrition, University of Fronteira Sul, Rodovia PR 182 Km 466, CEP 85770-000, Realeza, Paraná Postal Code 253, Brazil
Full list of author information is available at the end of the article

Capes, Science Direct, and Scientific Electronic Library Online (SciELO) were searched for English, Spanish or Portuguese-language articles. The crossing of "rheumatoid arthritis" with the following descriptors separately was used to accomplish this review: "adipokines", "leptin", "resistin", "visfatin", and "adiponectin". No exclusion criteria were established in view of the small number of articles regarding this current issue. The study selection process is described in Fig. 1.

Data extraction

The information sources were the results described in the articles selected. The following data were extracted from articles included in this review: authors, year of publication, study design, number of participants, disease characteristics, control groups and results regarding associations between each adipokine and markers of disease activity.

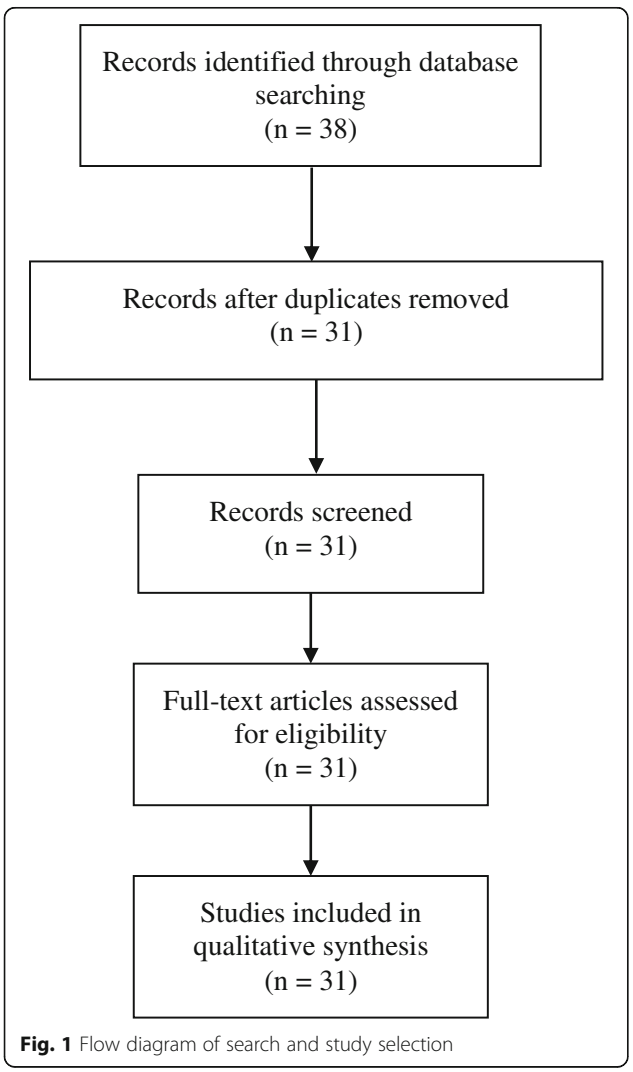

Fig. 1 Flow diagram of search and study selection

Results and discussion

Adipokines

Adipose tissue is a multifunctional organ responsible for lipid storage, thermogenesis, structural components and support of many organs such as joints, gastrointestinal tract and skin and nowadays also described as secretory and endocrine functions [7]. It is noteworthy in this context its role as an endocrine organ by synthesizing and secreting adipokines, which play an important role in the pathophysiology of insulin resistance, inflammation and atherogenesis [8, 9].

Leptin

Leptin is an adipokine produced in white adipose tissue. Discovered in 1994 [10], it is an *Ob* gene product [11], cloned and sequenced in mice and considered the adipokine responsible for the regulation of energy metabolism and homeostasis, as well as neuroendocrine functions [12]. It also assists the immunity and inflammation control through its receptor [13]. Thus, leptin is responsible for the regulation of various biological processes, being involved in the pathophysiology of many diseases. Leptin is considered a proinflammatory adipokine since it stimulates production of cytokines such as TNF-α, IL-6 and reactive oxygen species, and induces the production of CC chemokines by macrophages and alters the T helper (Th)1 / Th2 profile [13].

Paz-Filho et al. (2012) [14] described molecular mechanisms and pro-inflammatory systemic effects of leptin. It acts through its Ob receptor triggering inflammatory responses together with infectious and inflammatory stimuli of cytokines such as IL-1, lipopolysaccharide (LPS), and TNF-α, which may, in turn, increase levels of leptin. The interaction between leptin and inflammation are bidirectional, but all pro inflammatory since cytokines increases the synthesis and release of leptin, which in turn perpetuates the cycle of inflammation.

Leptin showed a significant effect on increasing the expression of Th1 cytokines. Experimental studies on mice demonstrated that these animals showed less severe stages of induced RA with lower levels of IL-1B and TNF-α in the synovial fluid and reduction in T-cell proliferative response induced by antigen [14]. However, clinical studies revealed paradoxical results about the effects of endogenous leptin in protecting joints in severe forms of erosive RA in humans [15].

In the last two decades, several studies have described the action of leptin in RA [16], leading researchers near to assume the hypothesis that this hormone has a key role in rheumatic diseases. [17] Thus, leptin levels may be a risk factor for the pathogenesis of RA [18].

Olama et al. (2012) [15] evaluated the ratio of synovial and serum leptin in patients with RA and found that the local utilization of leptin at the joint cavity has a

protector role against the destructive course of RA. Rho et al. (2010) [19] also examined the hypothesis that the adipokines could influence insulin resistance and coronary atherosclerosis in patients with RA. Leptin was positively associated with insulin resistance assessed by Homeostasis Model Assessment - Insulin Resistance (HOMA-IR), even after adjusting for age, race, sex, body mass index (BMI), traditional cardiovascular risk factors and inflammation mediators. Targońska-Stepniak et al. (2010) [20] assessed leptin levels in patients with RA and demonstrated positive correlation between leptin levels and Disease Activity Score (DAS)-28. Yoshino et al. (2011) [21] found leptin levels significantly higher in RA patients compared to controls, and this adipokine correlated positively with C-Reactive Protein (CRP) levels, suggesting that leptin can act as a proinflammatory in this disease. On the other hand, Kontunen et al. (2011) [22] showed that leptin levels were increased only in patients with RA and concomitant diagnosis of metabolic syndrome (MetS).

Kang et al. (2013) [23] demonstrated that TNF-α was positively associated to leptin and the latter was associated with various metabolic risk factors, including insulin resistance. Bustos Rivera-Bahena et al. (2015) [24] evidenced that circulating levels of leptin correlate positively with clinical activity of RA, regardless of BMI. However, Xibille-Friedmann et al. (2015) [25] concluded that in a short term basal levels of leptin may predict disease activity independent of BMI. However, when submitted to treatment, this only occurred in patients with normal body weight.

Tian et al. (2014) [26] reported a review in which 23 studies were analyzed. The following results were obtained: 13 studies showed increased leptin levels; 8 studies did not demonstrate any significant difference and 2 had reduced leptin levels when compared to control subjects. Therefore, most of the studies have found higher levels of leptin in patients with RA, showing a possible role in the regulation of joint damage, and suggested that more studies are needed to understand the mechanisms of action of this adipokine. A meta-analysis conducted by Lee e Bae (2016) [27] confirmed these data showing that circulating levels of leptin were significantly higher in patients with RA with a positive correlation between this hormone and RA activity.

Despite the evidence demonstrated, some studies do not corroborate these associations. Allam e Radwan (2012) [28] and Abdalla et al. (2014) [29] found that although serum leptin level was significantly higher in RA patients than in control group, there was no correlation with clinical and laboratory markers of disease activity. Mirfeizi et al. (2014) [30] also stated that leptin has no effect on the process of joint damage in RA patients. Oner et al. (2015) [31] did not find any correlation between disease activity and serum leptin levels, indicating that this adipokine is not a good biomarker to monitor inflammation in RA.

Thus, leptin seems to have a role in the pathophysiology of RA and comorbidities associated, such as obesity and metabolic syndrome. Leptin is considered a pro inflammatory adipokine by the great majority of authors who suggest a predominantly deleterious action on the joint. Only one survey showed that increased levels of leptin can act as a protective factor against the destructive course of RA.

Table 1 summarizes the main findings of leptin in RA patients.

Resistin

Isolated in rodents, resistin was first described in 2001. It is a protein rich in cysteine, compounded by 108 amino acids, called RELMs (resistin-like molecules) also known as FIZZ 332 [32]. In humans, it is originated mainly from circulating monocytes and macrophages [33].

It was initially correlated to the pathogenesis of insulin resistance in obesity and some cardiovascular diseases (CVD) but now is also considered an important link between obesity and inflammation [34]. Resistin has been found in areas of inflammation and seems to be mediated by IL-6 and TNF α [35].

Due to its implication in inflammation processes, the involvement of resistin in the pathogenesis of RA has been investigated. Kassem et al. (2010) [36] studied if there is a role of resistin in the pathogenesis of RA by investigating possible correlations between resistin concentration in serum and synovial fluid with disease activity and radiographic joint damage. The authors' results supported the hypothesis that resistin is involved in the pathogenesis of RA and suggested serum resistin as a good marker of prognosis of the disease in RA patients. Yoshino et al. (2011) [21] compared serum resistin levels from RA patients and healthy control subjects. The authors found that the level of resistin in serum did not differ between patients and controls, but observed that serum resistin were positively associated with CRP levels in RA patients, suggesting a pro inflammatory action of this cytokine.

Kontunen et al. (2011) [22] reported that high levels of resistin are associated with RA, regardless of the presence of MetS. Fadda et al. (2013) [37] compared resistin levels in serum and synovial fluid of patients with RA and osteoarthritis and found higher levels in patients with RA. This result indicates a possible role of resistin in the pathogenesis of inflammatory rheumatic diseases. The high levels of this adipokine in the synovial fluid could suggest a

Table 1 Studies investigating the association of leptin and rheumatoid arthritis in humans

Authors	Study design	Subjects	Results/outcomes
Rho et al. (2010) [19]	Cross-sectional study evaluating correlation between HOMA-IR and serum adipokine levels.	169 RA patients	Positive correlation between serum leptin and insulin resistance.
Targońska-Stepniak et al. (2010) [20]	Cross-sectional study evaluating correlation between disease activity and serum adipokine levels.	80 RA patients	Positive correlation between serum leptin and DAS28.
Yoshino et al. (2011) [21]	Case-control study evaluating correlation between inflammation markers and serum adipokine levels.	141 RA patients 146 controls without RA	Positive correlation between serum leptin and CRP.
Kontunen et al. (2011) [22]	Cross-sectional study evaluating correlation between serum adipokines levels and markers of inflammation and MetS.	54 RA patients, 20 with MetS	Increased levels of serum leptin observed only in patients with MetS.
Olama et al. (2012) [15]	Case-control study evaluating differences between serum leptin and synovial/serum leptin ratio.	40 RA patients 30 controls without RA	Inverse correlation between leptin concentration and protection of joints in severe RA.
Allam e Radwan (2012) [28]	Case-control study evaluating correlation between serum leptin levels and disease activity.	37 RA patients 34 controls without RA	No correlation between leptin levels and disease activity.
Kang et al. (2013) [23]	Cross-sectional study evaluating correlation between adipokine levels, inflammation markers, insulin resistance and atherosclerosis.	192 RA patients	Positive correlation between serum leptin and TNF-α and metabolic risk, including insulin resistance
Mirfeizi et al. (2014) [30]	Cross-sectional study evaluating correlation between adipokine levels and radiographic joint damage.	54 RA patients (29 with erosion and 25 without erosion)	No differences in serum leptin between the two groups.
Abdalla et al. (2014) [29]	Case-control study evaluating correlation between serum leptin levels and clinical manifestations of disease activity.	60 RA patients 30 healthy controls	No correlation between leptin levels and clinical and laboratorial markers of disease activity.
Bustos Rivera-Bahena et al. (2015) [24]	Cross-sectional study evaluating correlation between adipokine levels and disease activity.	121 RA patients	Positive correlation between serum leptin and disease activity.
Xibille-Friedmann et al. (2015) [25]	Cohort study evaluating if baseline levels of adipokines may predict disease activity or response to treatment.	127 RA patients after 6 months of follow up; 91 after 1 year of follow up; 52 after 2 years of follow up	Positive correlation between serum leptin and prevention of disease activity progression.
Oner et al. (2015) [31]	Case-control study evaluating correlation between serum leptin levels and disease activity.	106 RA patients 52 healthy controls 37 osteoarthritis patients	No correlation between serum leptin and disease activity.
Lee e Bae (2016) [27]	Meta-analysis evaluating correlation between serum leptin levels and disease activity.	13 studies: 648 RA patients 426 controls without RA	Leptin levels significantly higher in RA patients and weak positive correlation between leptin levels and disease activity.

RA = rheumatoid arthritis; HOMA-IR = homeostatic model assessment-insulin resistance; DAS28 = Disease Activity Score-28; CRP = C-reactive protein; TNF-α = tumor necrosis factor-α; Metabolic Syndrome = MetS

bad prognosis for progression of RA, but the authors point out that more studies are needed to confirm if resistin is a good marker to evaluate the progression of this disease. Kang et al. (2013) [23] reinforced this hypothesis. The authors found an association between resistin levels and inflammatory markers in patients with RA. Recently, Bustos Rivera-Bahena et al. (2015) [24] demonstrated that resistin levels correlated positively with clinical manifestations of disease activity in patients with RA, albeit of patient body mass index. Huang et al. (2015) [38] in a meta-analysis concluded that serum resistin levels were significantly higher in RA patients compared to control group.

However, some authors did not show significant associations between serum resistin and HOMA-IR, nor differences between serum and synovial fluid resistin levels between RA patients and controls [19]. Al-Kady et al. (2010) [39] after studying the levels of resistin in of RA patients found no significant differences in resistin levels between RA patients and controls. Hammad et al. (2014) [40] also found no correlation between serum levels of resistin with clinical or laboratory markers in RA patients.

Thus, there is an important role of adipokines in the pathogenesis of obesity, CVD and inflammatory processes. The pro inflammatory action of resistin was observed in most studies of patients with RA, which

suggest that this adipokines is a good marker to assess the progression of this disease.

Table 2 summarizes the main findings of resistin in RA patients.

Visfatin

Also known as PBEF (pre-B-cell colony-enhancing factor) or Nicotinamide Phosphoribosyltransferase (Nampt) [41], visfatin is a protein with molecular weight of 52 kDa, first described by Samal et al. (1994) [42]. It is primarily found in liver, bone marrow and muscle tissue, but also produced by adipose tissue and secreted by macrophage [43]. Its production is influenced by TNF-α, IL-6, Toll-like receptor (TLR) and chemokines [44]. Stofkova (2010) [45] reports that visfatin may contribute to inflammation processes, triggering production of cytokines and activation of nuclear factor kappa beta (NF-κβ). Thus, some studies have suggested some relation between this adipokine and the pathogenesis of type 2 diabetes and obesity [46] and increased cardiovascular risk [47].

Other studies have demonstrated a correlation between serum and synovial fluid levels of visfatin and the pathogenesis of RA [13, 41, 48, 49]. This adipokine can act as a regulator of inflammation and the destruction process of joints [35] and induce stimulation of great quantities of chemokines [50], thus possibly contributing to the inflammatory state of RA. However, its association to disease activity is not yet fully known [51].

Alkady et al. (2011) [52] showed that visfatin levels correlated with disease activity and may be involved in the progression of RA. Khalifa et al. (2013) [53] suggested that visfatin has a role in the pathogenesis of RA, and it may be considered as a marker of the disease and the radiographic bone lesion score. Therefore, it can be a potential therapeutic target for RA. El-Hini et al. (2013) [54] demonstrated positive and significant correlation between visfatin and insulin resistance and also with serum cholesterol, low density lipoprotein cholesterol (LDL-c) and triglycerides.

Table 2 Studies investigating the association of resistin and rheumatoid arthritis in humans

Authors	Study design	Subjects	Results/outcomes
Kassem et al. (2010) [36]	Case-control study evaluating correlation between serum and synovial resistin and inflammation markers, disease activity and radiographic joint damage.	30 RA patients 15 healthy controls	Significant correlation between serum resistin levels and CRP, ESR, rheumatoid factor and disease activity. Also considered a good prognostic marker of RA.
Rho et al. (2010) [19]	Cross-sectional study evaluating correlation between HOMA-IR and serum adipokine levels.	169 RA patients	No significant correlation between serum resistin and insulin resistance.
Al-Kady et al. (2010) [39]	Case-control study evaluating correlation between serum and synovial liquid adipokines and disease activity.	70 RA patients 30 controls	No differences between groups in serum resistin, but it was observed synovial liquid resistin levels significantly higher in patients with active disease.
Yoshino et al. (2011) [21]	Case-control study evaluating correlation between inflammation markers and serum adipokines levels.	141 RA patients 146 controls	No differences in serum resistin between groups, but in RA patients it was positively associated with CRP levels.
Kontunen et al. (2011) [22]	Cross-sectional study evaluating correlation between serum adipokine levels and markers of inflammation and MetS in RA.	54 RA patients, 20 with MetS	Increased levels of resistin were associated with RA irrespective of the presence of MetS.
Fadda et al. (2013) [37]	Case-control study comparing serum and synovial liquid resistin in patients with RA and osteoarthritis.	25 RA patients 25 osteoarthritis patients	Significant correlation between synovial liquid resistin and rheumatoid factor and ACPA, indicating a bad prognosis of disease.
Kang et al. (2013) [23]	Cross-sectional study evaluating correlation between adipokines levels, inflammation markers, insulin resistance and atherosclerosis.	192 RA patients	Significant correlation between serum resistin and inflammation markers ESR and CRP and disease duration.
Hammad et al. (2014) [40]	Case-control study comparing serum resistin in RA patients and a control group and its association to disease activity.	30 RA patients 30 controls	No correlation between serum resistin levels and clinical and laboratorial markers of disease activity.
Bustos Rivera-Bahena et al. (2015) [24]	Cross-sectional study evaluating correlation between adipokines levels and disease activity.	121 RA patients	Positive correlation between resistin levels and disease activity.
Huang et al. (2015) [38]	Meta-analysis evaluating correlation between serum resistin levels and RA.	8 studies with RA: 620 RA patients 460 controls	Serum resistin levels were significantly higher in patients with RA.

RA = rheumatoid arthritis; CRP = C-reactive protein; TNF-α = tumor necrosis factor-α; ESR = erythrocyte sedimentation rate; ACPA = anti-citrullinated protein antibody; HOMA-IR = homeostatic model assessment-insulin resistance; Metabolic Syndrome = MetS

Additionally, the disease activity score was positively correlated with visfatin.

Sglunda et al. (2014) [55] observed that visfatin levels in serum were significantly higher in RA patients compared to healthy individuals and suggested that reduction in visfatin concentrations could reduce disease activity in patients at early stage of RA. They also found positive association between this adipokine and elevated levels of total cholesterol, but not with the atherogenic index. Mirfeizi et al. (2014) [30] found that serum levels of visfatin in RA patients with radiographic joint damage were significantly higher than in patients without joint damage.

Nonetheless, Rho et al. (2010) [19] did not evidence relationship between visfatin and insulin resistance nor coronary atherosclerosis in patients with RA and Meyer et al. (2013) [56] did not show any correlation between serum levels of visfatin and radiographic progression of the disease.

Table 3 summarizes the main findings of visfatin in RA patients.

Adponectin

Adiponectin is an anti-inflammatory adipokine compounded by 244 amino acids and is produced and secreted mainly by adipocytes. [57, 58] Studies suggest that monomeric form of adiponectin appears to occur only in adipocytes, but there are three forms of adiponectin circulating in the body: trimmers (low molecular weight, LMW), hexamers (middle molecular weight, MMW) and multimers (high molecular weight, HMW) are the plasma circulating forms of adiponectin [58]. The receptors are AdipoR1and AdipoR2, respectively present at skeletal muscles and liver [59].

Several studies have demonstrated the role of this important anti-inflammatory cytokine in obesity, diabetes mellitus type 2, atherosclerosis and metabolic syndrome, being the highest levels a protective factor for these diseases [35, 60–62].

Paradoxically, in the pathogenesis of rheumatoid arthritis adiponectin seems to have proinflammatory effects in the joints, because its ability to stimulate the secretion of inflammatory mediators [63] and may also be associated to disease activity [52]. Scotece et al. (2012) [64] described the major effects of increased synovial and circulating levels of adiponectin in RA. They concluded that adiponectin in synovial fibroblasts induced prostaglandin (PG)E2, IL-6, IL-8, matrix metalloproteinase (MMP)-1 and MMP-13; in human chondrocytes induced nitric oxide (NO), IL-6, MMP-3, MMP-9, monocyte chemoattractant protein (MCP)-1 and IL-8 and promoted inflammation by increasing TNF-α, IL-6 and IL-8.

Krysiak et al. (2012) [65] suggested that these different actions can be explained by different mechanisms: LMW adiponectin has anti-inflammatory activities, while the HMW adiponectin has proinflammatory activities. However, Frommer et al. (2012) [66] showed a proinflammatory and destructive role of all isoforms

Table 3 Studies investigating the association of visfatin and rheumatoid arthritis in humans

Authors	Study design	Subjects	Results/outcomes
Rho et al. (2010) [19]	Cross-sectional study evaluating correlation between HOMA-IR and serum adipokine levels.	169 RA patients	No correlation between visfatin levels and IR
Alkady et al. (2011) [52]	Case-control study evaluating correlation between serum and synovial liquid adipokines and disease activity.	70 RA patients 30 controls	Positive correlation between serum visfatin levels and disease activity.
Khalifa et al. (2013) [53]	Case-control study evaluating correlation between serum visfatin and inflammation markers.	60 RA patients 20 controls	Positive correlation between visfatin levels and IL-6, CRP, ERS, TNF-α and DAS-28 in RA.
El-Hini et al. (2013) [54]	Case-control study evaluating metabolic disorder and its association with clinical characteristics of RA patients.	40 RA patients 40 controls	Positive correlations between serum visfatin levels and IR, cholesterol, triglycerides and LDL-C.
Meyer et al. (2013) [56]	Cohort study evaluating serum adipokine levels and radiographic progression of RA.	632 RA patients at early stage of disease and 159 with unspecific arthritis	No correlation between visfatin levels and progression of RA.
Sglunda et al. (2014) [55]	Prospective study evaluating visfatin level and its relationship with disease activity and serum lipids.	40 patients with early, treatment-naïve RA 30 controls	Correlation between visfatin levels and disease activity and reduced levels after treatment.
Mirfeizi et al. (2014) [30]	Cross-sectional study evaluating correlation between serum adipokines levels and radiographic joint damage.	54 RA patients (29 with erosion and 25 without erosion)	The levels of visfatin were higher in patients with radiographic joint damage and dependent on the duration of the disease.

RA = rheumatoid arthritis; IR = insulin resistance; MetS = metabolic syndrome; IL-6 = interleukin-6; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; DAS28 = Disease Activity Score-28; TNF-α = tumor necrosis factor α; LDL-C = low-density lipoprotein cholesterol

of adiponectin in patients with RA, suggesting a much more harmful than beneficial action of adiponectin in chronic inflammatory diseases. Several studies evidenced association of adiponectin in radiographic progression of RA [67, 68]. Thus, serum adiponectin levels could be a good biomarker to evaluate the early stages of disease progression [56]. However, this association was not mediated by the selective effect of HMW adiponectin. [69] Recently, Skalska and Kontny (2016) [18] observed that HMW and MMW adiponectins potentially stimulated the secretion of rheumatoid ASC (adipose-derived stem cells) in patients with RA, but did not exert a strong impact on ASC towards RA-FLS (fibroblast-like synoviocytes) and peripheral blood mononuclear cells.

Furthermore, Rho et al. (2010) [19] did not find any association between adiponectin levels and insulin resistance or coronary artery calcium score. Yoshino et al. (2011) [21] also observed higher levels of adiponectin in serum of RA patients, but it was negatively associated with CRP levels. Bustos Rivera-Bahena et al. (2015) [24] did not evidenced association between adiponectin and disease activity and Chennareddy et al. (2016) [70] reported that despite serum levels of adiponectin are higher in RA patients than in controls there was no correlation with disease activity, duration, BMI and waist-to-hip ratio.

Despite the protective effect of adiponectin in the pathogenesis of obesity, diabetes mellitus, atherosclerosis, and metabolic syndrome, it is unclear whether this effect is reproduced in RA. Several studies emphasize that adiponectin appears to play a pro inflammatory role in the pathogenesis of RA, particularly in the joints, by stimulating the secretion of inflammatory mediators. In this scenario, it highlights the importance of developing new research elucidating the real role of adipokines in the pathogenesis of RA.

Table 4 summarizes the main findings of adipnectin in RA patients.

Conclusion

In recent years, it has been studied the importance of adipokines in the pathogenesis of RA, however the results are still conflicting and the exactly role of adipose tissue in RA is not yet fully understood. Despite studies have been demonstrating the implications of adipokines in the pathophysiology of autoimmune diseases, including RA, it is not yet clear their role in the progression of disease. It is noteworthy the complex pathophysiology of this disease, thus requiring better knowledge about the mechanisms of action of these adipokines in RA as well as the changes that drugs can promote in the circulating levels of these adipokines in these patients.

Table 4 Studies investigating the association of adiponectin and rheumatoid arthritis in humans

Authors	Study design	Subjects	Results/outcomes
Rho et al. (2010) [19]	Cross-sectional study evaluating correlation between HOMA-IR and serum adipokine levels.	169 RA patients	No correlation between adiponectin and insulin resistance.
Alkady et al. (2011) [52]	Case-control study evaluating correlation between serum and synovial liquid adipokines and disease activity.	70 RA patients 30 controls	Positive correlation between serum and synovial adiponectin levels and disease activity.
Yoshino et al. (2011) [21]	Case-control study evaluating correlation between inflammation markers and serum adipokine levels.	141 RA patients 146 controls	No correlation between serum adiponectin levels and CRP.
Giles et al. (2011) [67]	Prospective study evaluating association of serum adipokine levels with progression of radiographic joint damage in patients with rheumatoid arthritis.	152 RA patients	Positive correlation between serum adiponectin levels and erosive joint destruction.
Klein-Wieringa et al. (2011) [68]	Cohort study evaluating baseline adipokine levels to predict radiographic progression of RA over a period of 4 years.	253 RA patients	Positive correlation between serum levels of adiponectin and radiographic progression of 4 RA.
Meyer et al. (2013) [56]	Cohort study evaluating serum adipokines levels and radiographic progression of RA.	632 RA patients at early stage of disease and 159 with unspecific arthritis	Positive association between serum adiponectin levels and radiographic progression of RA at early stage.
Bustos Rivera-Bahena et al. (2015) [24]	Cross-sectional study evaluating correlation between adipokines levels and disease activity.	121 RA patients	No correlation between serum adiponectin and clinical activity of RA, but negative correlation with TNFα and positive correlation with IL-1β.
Chennareddy et al. (2016) [70]	Cross-sectional study evaluating the serum concentrations of adiponectin and its impact on disease activity and radiographic joint damage.	43 RA patients 25 controls	Increased levels of serum adiponectin in RA, but no correlation with erosive and non-erosive dis ease, disease duration, BMI, waist-hip ratio and disease activity.

RA = rheumatoid arthritis; IR = insulin resistance; CRP = C-reactive protein; BMI = body mass index

Abbreviations

ACPA: Anti–citrullinated protein antibody; ASC: Adipose-derived stem cells; BMI: Body mass index; CRP: C-reactive protein; CVD: Cardiovascular diseases; DAS: Disease Activity Score; FLS: Fibroblast-like synoviocytes; HMW: High molecular weight; HOMA-IR: Homeostasis Model Assessment - Insulin Resistance; IL: Interleukin; LDL-c: Low density lipoprotein cholesterol; LMW: Low molecular weight; LPS: Lipopolysaccharide; MCP: Monocyte chemoattractant protein; MetS: Metabolic syndrome; MMP: Matrix metalloproteinase; MMW: Middle molecular weight; Nampt: Nicotinamide phosphoribosyltransferase; NF-κβ: Nuclear factor kappa beta; NO: Nitric oxide; PBEF: Pre-B-cell colony-enhancing factor; PG: Prostaglandina; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RA: Rheumatoid arthritis; RELM: Resistin-like molecules; RF: Rheumatoid factor; SciELO: Scientific Electronic Library Online; Th: T helper; TLR: Toll-like receptor; TNF: Tumor necrosis factor

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Authors' contributions

ECSF and FTR made substantial contributions to acquisition and interpretation of data, and writing the manuscript. ANCS and ID contributed to conception of the study, and revising it critically. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author details

[1]Postgraduate Program, Health Sciences Center, State University of Londrina, Londrina, Paraná, Brazil. [2]Postgraduate Program, Experimental Pathology, State University of Londrina, Londrina, Paraná, Brazil. [3]Department of Pathology, Clinical Analysis and Toxicology, University Londrina, Londrina, Paraná, Brazil. [4]Department of Internal Medicine, University of Londrina, Londrina, Paraná, Brazil. [5]Department of Nutrition, University of Fronteira Sul, Rodovia PR 182 Km 466, CEP 85770-000, Realeza, Paraná Postal Code 253, Brazil.

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