Review

Adipokines in connective tissue diseases

K. Sawicka, D. Krasowska

Department of Dermatology, Venereology and Pediatric Dermatology, Medical University of Lublin, Poland.

Karolina Sawicka, MD
Dorota Krasowska, MD, PhD

Please address correspondence to:
Karolina Sawicka, MD,
Department of Dermatology,
Venereology and Pediatric Dermatology,
Medical University of Lublin,
13 Radziwiłłowska str.,
20-080 Lublin, Poland.
E-mail: k.sawicka10@gmail.com

Received on October 6, 2015; accepted in revised form on May 16, 2016.

Clin Exp Rheumatol 2016; 34: 1101-1112.

Key words: adipokines, connective tissue diseases, leptin, resisitin, adiponectin

Competing interests: none declared.

ABSTRACT

Adipokines, pleiotropic molecules produced by white adipose tissue (WAT) have attracted the attention of scientists since 1994. The role of adipokines in metabolic syndrome is known and fixed. Adipokines exerting a variety of metabolic activities have contributed to the ethiopathogenesis and the consequences of metabolic syndrome. Furthermore, adipokines are involved in the regulation of inflammatory processes and autoimmunity in the light of pathogenesis of connective tissue diseases. Given some evidence for the influence of adipokines in metabolic syndrome, there may be a link between CVDs and rheumatic diseases. This review provides an overview of the literature focusing on the role of adipokines in rheumatic diseases by putting special emphasis on the potential role of leptin, resistin, adiponectin, chemerin, visfatin and novel adipokines in connective tissue diseases.

Introduction

In 1994, the year in which Zhang *et al.* discovered leptin, there was a breakthrough in the perception of adipose tissue functions (1). Since then white adipose tissue (WAT) has been considered as an active endocrine and immune organ, which has a significant regulatory function and influence on maintaining systemic homeostasis, participates in a number of metabolic, immunologic, inflammatory, fibrogenesis processes and synthesises biologically active substances – adipokines. Hormones of white adipose tissue influence numerous immune system cells: lymphocytes, macrophages, fibroblasts. It is known that adipocytes secrete approximately 50 different adipokines (2). Among cytokines produced by adipose tissue, the most well-known are the following: adiponectin, leptin, resistin and, to a lesser extent, visfatin, chemerin and others. There are numerous articles on the study of these substances in rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, osteoarthritis and systemic sclerosis. The present paper offers an extensive review of selected WAT hormones in connective tissue systemic diseases.

Leptin

Leptin is a 16-kDa non-glycosylated peptide hormone produced primarily by adipose tissue cells. The discovery of leptin in 1994 revolutionised the importance of white adipose tissue, which is not only an energy storage but also a significant endocrine and regulatory organ. Leptin is encoded by *obese gen* (*ob*) located on chromosome 7q31.3. Leptin synthesis occurs mainly in adipocytes, but also in the hypothalamus, pituitary gland, skeletal muscles, mammary gland and epithelium of the alimentary tract. The main role of leptin is the influence on metabolism and appetite. Negative energy balance leads to a drop in leptin synthesis and secretion of appetite enhancing neurotransmitters such as: neuropeptide Y, orexin, galanin and melanin-concentrating hormone (MCH) (3). Leptin secretion exhibits daily variability, with the peak during night hours [3]. Leptin production depends on the level of insulin, sexual hormones, interleukin 1, TNF-α and other inflammatory mediators. Leptin exerts its biological action through activation of its receptor (ObR). This receptor belongs to the type 1 cytokine superfamily receptor members, and has three different types: long (Ob-Rb), short (Ob-Ra, c, d, f) and soluble (Ob-Re), named OBR, LEPR or LR. Leptin receptors can be found in immune cells, macrophages, T cells, NK and polymorphonuclear cells. The intracellular domain of OBRb belongs to Janus kinase signal transduction system (JAK2/STAT3). This is the key physiological

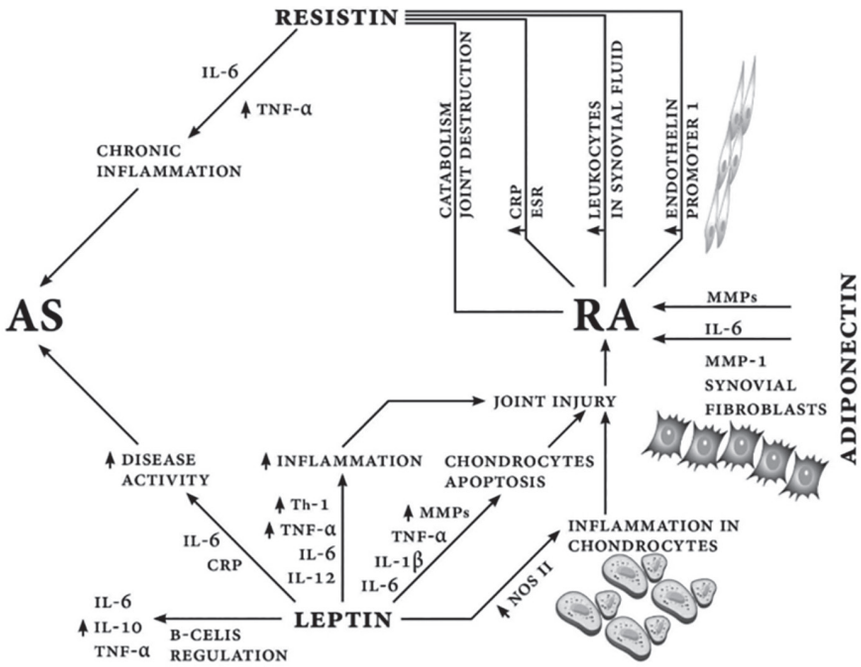
and metabolic pathway (4, 5). Not only JAK/STAT, but also MAPK/ERK and AMP-activated protein kinase (MAPK) and PI3K/Akt are involved in leptin signalling and molecular mechanisms (5). Leptin plays a modulatory, and basically proinflammatory role. This adipokine has an impact on immunity by activation a proliferation of macrophages and maturation of dendritic cells, it downregulates apoptosis of neutrophils, eosinophils and dendritic cells (5). Moreover, leptin exhibits similar structural and functional characteristics tothe IL-6 cytokine family, increases an inflammation by regulation of Th1 (lymphocytes T helper type 1) dependent response and production of pro-inflammatory cytokines by macrophages such as TNF-α, IL-6 and IL-12 and induces CD69, CD25, CD38 and CD71 (5-7). Leptin stimulates secretion and maturation of thymocytes and activation of Th1 and B cells. It also inhibits production of regulatory T cells. Leptin stimulates the production of intrerferone (IFN-γ) and IL-2 in T-lymphocytes (8). Furthermore, leptin has protective properties toward lymphocytes T against corticosteroid induced apoptosis, increases expression of adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1) and very late antigen-2 (VLA2) which contributes to activation and migration of the cells to the inflammation site (9). Regarding B cells and immunoregulation, leptin modulates them to produce cytokines such as IL-6, IL-10 and TNF-α by activating Janus kinase 2/signal transducer and activator of transcription -3 (JAK2/STAT-3) and p38MAPK/extracellular-regulated kinase ½ (ERK1/2) signalling pathways (10).

Some authors report that leptin can be an important factor linking obesity, the metabolic syndrome and cardiovascular disorders. It is involved in body weight regulation and has proatherogenic role (11). Patients with metabolic syndrome (MetS) had higher leptin levels compared with individuals without MetS. What is more, leptin was strongly correlated with insulin sensitivity and waist circumference. Serum leptin levels predict MetS development independently from obesity (12). Yadav *et al*. showed a significant positive correlation of serum leptin levels with insulin resistance, triglycerides and a negative correlation with HDL-cholesterol (13). Due to the fact that leptin induces chondrocyte apoptosis in cartilage and increases metalloproteinase activity and similarly to interferon γ and IL-1, activates nitric oxide synthase II, acts proinflammatory in chondrocyte cells (14) (Fig. 1). This mechanism is responsible for leptin participation in pathogenesis of connective tissue systemic diseases, especially in rheumatoid arthritis (RA). Furthermore, it has been noted that leptin exhibits proinflammatory and proatherogenic action in the course of RA (11). Tian *et al*. indicated increased serum leptin concentrations in patients with RA. Therefore, it could be possible to treat patients with RA and reduce the damage of the joints by blocking leptin signal path (5). Targońska-Stępniak *et al*. reported higher serum leptin levels among RA patients with erosive joint disease compared to those without erosions. It may indicate that high serum levels of leptin may increase the risk of progressive joint destruction (11). Yoshino *et al*. stated that serum leptin levels were related to CRP levels in RA patients (15). However, some studies have not stated the differences in the serum leptin levels among RA patients compared to controls (16-19). Anders *et al*. have not observed the correlation between serum leptin levels and disease activity in RA patients (20). Due to high level of TNF-α in RA, scientists assessed correlation between anti-TNF therapy in RA patients and serum leptin levels. TNF-α blockers are effective in treatment of RA patients and reduce CV (cardiovascular) mortality comparing to disease modifying anti-rheumatic drugs. However, the beneficial effect of anti-TNF-α therapy and decreased CV mortality in RA patients seem not to be mediated by serum leptin levels (21). Gonzalez-Gay *et al*. reported about 33 patients with RA on periodical treatment with anti-TNF therapy. The study conducted by the authors shows a positive correlation between body mass index of RA patients and serum leptin levels (21). Data on the role of leptin as a predictor of disease activity in RA are controversial. On the one hand, there was no correlation between serum leptin levels and most clinical and laboratory parameters of disease activity and inflammation. Actually, in the patients with severe RA, circulating leptin concentrations constitute a manifestation of adiposity as it is observed in subjects without RA (21). Härle *et al*. also reported that serum leptin concentrations in RA patients were not decreased by 12 weeks anti-TNF-α treatment (adalimumab) (19). On the other hand, Xibillé-Friedmann *et al*. examined in their study whether leptin serum levels can predict disease activity or response to treatment with NSAIDs (non-steroid anti-inflammatory drugs, prednisone or DMARDs (disease-modifying anti-rheumatic drugs) in RA patients at regular follow-up. The authors found that baseline leptin levels can predict disease activity in all RA patients (22).

To sum up, the results of different clinical studies suggest that leptin may be engaged in the inflammation and joint damage of RA patients.

The role of leptin in ankylosing spondylitis (AS) is unclear. Park *et al*. found association between leptin levels, CRP, IL-6 and disease activity in AS patients (23). For instance, Miranda-Filloy *et al*. assessed leptin concentrations in non-diabetic AS patients treated with anti-TNF-α therapy. The authors discovered no correlation between leptin concentrations and disease duration, ESR, C-reactive protein. There was also no change in leptin levels after infliximab therapy. In conclusion, in non-diabetic patients with ankylosing spondylitis on treatment with the anti-TNF-α-blocker infliximab, leptin did not correlate with disease activity or systemic inflammation (24).

There are reports in which high leptin concentrations run the risk of increased connective tissue disease morbidity. Garcia-Gonzales showed increased leptin concentration in women with systemic lupus erythematosus (SLE) compared to healthy women. Patients with SLE had no association between leptin levels and SLEDAI score, age, duration of disease, or prednisone doses (25-27). Chung *et al*. tested the hypothesis that concentrations of leptin were altered in SLE and associated with coronary



IL-6 – Interleukin-6
IL-10 – Interleukin-10
IL-12 – Interleukin-12
CRP – C-reactive Protein
ESR – Erythrocyte Sedimentation Rate
TNF-α – Tumor Necrosis Factor-α
NOS II – Nitric Oxide Synthase II
MMP-1 – Matrix Metalloproteinase-1
MMPs – Matrix Metalloproteinases

Fig. 1. Schematic representation of effects of leptin, resistin and adiponectin on pathogenetic processes in rheumatoid arthritis and ankylosing spondylitis. Adipokines regulate disease acitivity, inflammation and joint injury in rheumatic diseases.

atherosclerosis, insulin resistance and inflammation. Patients with SLE had increased serum concentrations of leptin and higher concentrations of leptin were associated with insulin resistance, BMI and CRP in patients with SLE (26). Vadacca *et al*. assessed leptin levels and its relationship with stiffness parameters (diameter changes of the carotid artery between systole and diastole during a cardiac cycle in a colour-coded duplex sonography) and disease activity index (SLEDAI) in women with SLE. Median leptin levels were higher in SLE patients compared with healthy controls and correlated with disease activity (SLEDAI) and vascular stiffness (27).

Taking everything into account, these data may suggest a significant proinflammatory role of leptin in SLE patients and its association with clinical features of metabolic syndrome.

Studies on leptin in systemic sclerosis (SSc) are diverging. Winsz-Szczotka *et al*. obtained decreased leptin concentrations in serum of patients with SSc and postulated a clear link between leptinaemia and disease duration, ESR level and Rodnan skin score (28). Similar results were obtained by Kotulska *et al*. who revealed decreased leptin concentrations in blood serum of patients with SSc. The authors hypothesised that corticosteroids, thyroid hormones, the autonomic nervous system, the renin-angiotensin system may affect serum leptin level, or what is interesting, an impairment of alimentary track may be responsible for this phenomenon (29, 30). Contrarily, Pehlivan *et al*. recorded increased serum leptin concentrations in patients suffering from SSc compared to control group. Moreover, there was a positive correlation between leptin and TNF-α, ESR and BMI. Intriguingly, leptin concentrations in patients with SSc were higher compared to healthy people with the same BMI. It is also worth paying attention to the fact that increased leptin concentrations lead to decrease in appetite and cachexia in patients with SSc (30).

To sum up, the role of letpin in SSc is controversial and requires further study. Taking into consideration other diseases connected with chronic inflammation like psoriasis, there is an interesting study of Pina *et al*. who assessed leptin levels in 29 non-diabetic patients with moderate-to-severe psoriasis who completed 6 months of therapy with anti-TNF-α adalimumab. In patients with moderate-to-severe psoriasis leptin levels correlated with metabolic syndrome features, CRP, insulin resistance and inflammation, but no significant changes in leptin concentrations during anti-TNF-α therapy were found (31).

Making provision for all the above-mentioned data, leptin may be involved in the development of connective tissue diseases and it may play an important role in the inflammation.

Resistin

Resistin is a 12,5kDa protein discovered in 2001 which belongs to the protein family FIZZ3 ("found in inflammatory zone 3"). Resistin gen (RETN) is located on chromosome 19p13. Transcription of this gene is induced by pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and lipopolysaccharide (LPS) and inhibited by PPARγ (peroxisome proliferator activated receptor γ). Resistin exists in two forms: as a heksamer or more bioactive trimer. Glucose metabolism modulating feature of resistin is associated with suppressor of cytokine signalling 3-SOCS3, which is inhibitor insulin transduction in adipocytes (32). Recently, TLRs4 were suspected to mediate resistin inflammatory responses in human cells, due to resistin receptor remains unknown (33). Glucocorticosteroids, growth hormone, thyroid hormone, vitamin A, pro-inflammatory cytokines and also insulin and glucose may have an effect on regulation of resistin gene expression (34). Moreover, resistin is secreted in chronic inflammation and participates in the development of inflammatory response. Higher resistin concentrations occur during infections. Significant correlation was established between resistin concentrations and inflammatory markers, *e.g*. C-reactive protein (35). What seems to be interesting the role of resistin in disease related to chronic inflammation processes, such as t.2 diabetes, chronic kidney disease and chronic infections (36).

Resistin increases VCAM-1, ICAM-1 expression, intensifies MCP-1 action and activates endothelium cells which release endothelin 1 (35). Resistin adversely affects endothelium function by increased production of peroxides which leads to impairment of blood vessel dilating (35). Furthermore, abnormalities in the course of angiogenesis were associated with the development of diseases such as coronary heart disease, malignancies, diabetes, chronic inflammation, atherosclerosis (35).

Resistin is responsible for maintaining carbohydrate homeostasis. Therefore it plays a significant role in the development of metabolic syndrome. Resistin may be a link between obesity and diabetes (37). Steppan *et al*. reported about association of increased resistin levels with obesity and visceral fat, insulin resistance, diabetes mellitus type 2, while others denied such information (37, 38). Interestingly, Norata *et al*. proposed the hypothesis concerning the role of resisitn and its association with inflammatory markers in development of MetS and its correlation with metabolic parameters like BMI, glucose, lipids as a secondary effect (39).

A role for resistin in pathology of RA was explored. Senolt *et al*. stated that resistin was connected with disease activity and joint destruction (40). Likewise, Bokarewa *et al*. investigated increased resistin concentrations in the synovial fluid and described a positive correlation between resistin and IL-6 concentrations and the number of leukocytes in the synovial fluid in RA patients (41). It can be suggested that resistin is produced in the inflamed joints (35). To confirm these data, Forsblad *et al*. reported the correlation of resistin levels with agonist of the IL-1 receptor in postmenopausal women with RA. Resistin was associated with increased inflammation, particularly by the acute-phase reactant IL-1Ra antagonising IL-1β, joint destruction and glucocorticosteroids (42). Schäffler *et al*. proved correlation between resistin serum levels in the blood serum and CRP, ESR and TNF-α in patients with RA. Furthermore, these scientists reported about increased levels of resistin in synovial fluid from RA patients compared to healthy patients (43). What is more, Gonzalez-Gay *et al*. showed that anti-TNF-α therapy (periodical treatment with infliximab) decreased resistin serum levels in patients with RA. The obtained results showed also strong association between serum resistin levels and markers of inflammation, particularly with CRP, but also supported a potential role of resistin in the inflammatory cascade in RA (44).

The role of resistin is assumed to be involved in AS pathogenesis. Kocabas *et al*. reported higher serum resistin levels in AS patients, but no correlation between resistin concentrations and ESR, CRP and BASDAI was observed (45). Similarly, Syrbe *et al*. found elevated serum resistin levels in 86 AS patients (46). Although anti-TNF-α therapy in AS patients has a beneficial effect, resistin levels and inflammatory markers were not changed during this therapy (47). Recent studies showed no correlation between resistin concentrations, disease activity and inflammatory markers in patients with AS, probably as a result of prolonged biological therapy (45, 47).

Additionally, resistin may act as a marker of inflammation in other rheumatic disorders like SLE. However, results seem to be contradictory. Almehed *et al*. described a positive correlation between serum resistin levels, general inflammation, bone loss and renal disease in patients with SLE compared to controls (48). What is more, Hutcheson *et al*. found increased resistin expression in both sera and urine from lupus nephritis (LN) patients compared to matched controls. Serum resistin, but not urine resistin, was correlated with parameters of renal dysfunction in LN. Serum resistin levels may be useful marker of renal dysfunction in LN patients, although further studies are necessary to determine if resistin has functional consequences in LN (49). In contrast, Huang *et al*. showed opposite results, finding no differences between serum resistin levels in SLE patients compared to healthy controls (50).

Furthermore, resistin plays an important role in pathogenesis of SSc. This adipokine causes endothelium dysfunction and affects the proliferation of endothelial cells in patients with SSc. Verma *et al*. demonstrated that resistin increases endothelin 1 promoter, the factor that causes vasoconstriction playing essential role in the pathogenesis of SSc (51). Olewicz-Gawlik *et al*. studying resistin concentration in the blood serum of 34 patients with SSc obtained significantly higher levels of this adipokine compared to control group (52). Moreover, Adrych *et al*. demonstrated elevated resistin concentrations as a possible cause of fibrosis in chronic pancreatitis. It may also suggest the potential role of resistin in the pathogenesis of fibrosis in SSc (53).

Moreover, a positive association between parameters of disease activity in psoriasis and resistin concentrations were disclosed among patients with moderate-to-severe psoriasis. Pina *et al*. observed a correlation between resistin and metabolic features and disease severity in psoriasis patients treated with anti-TNF-α therapy (31). A positive correlation between parameters of disease activity (BSA- body surface area and PASI- psoriasis area and severity index), CRP level and resistin concentrations were described (31).

Taking everything into consideration, many clinical studies indicate that resistin may act as an inflammatory mediator in connective tissue diseases.

Adiponectin

Adiponectin is biologically active protein described by Scherer *et al*. in 1995 (54). This hormone is built of 244 amino acids and has molecular weight of 33 kDa and it has sequences homologous to collagen type VIII, and X and C1q complement component. Adiponectin is coded by ACDC gene (APM1). Human serum contains three main adiponectin oligomers: of low (LMW), medium (MMW) and high (HMW) molecular weight. Adiponectin acts via two receptors, AdipoR1 found mainly in skeletal muscles and another AdipoR2 in liver. Transduction of the adiponectin signal by AdipoR1 and AdipoR2 involves the activation of AMPK (AMP-activated protein kinase) (55). A gene of the hormone is regulated on the transcription level by the PPAR (peroxisome proliferator activated receptor). What is more, adiponectin via the p38 MAPK

pathway induces IL-6 production and metalloproteinase-1 in synovial fibroblasts (56).

Not all mechanisms of adiponectin regulation have been understood so far, but it is known that adiponectin influences numerous metabolic processes and systemic homeostasis. One of the basic biochemical functions of the hormone is 5'AMP-activated protein kinase phosphorylation in muscles. Adiponectin increases insulin sensitivity of tissues. Additionally, it stimulates phosphorylation and inactivation of acetyl-CoA carboxylase, intensifies fatty acid beta-oxidation in skeletal muscles. It stimulates translocation of glucose transporter GLUT-4, thus it increases glucose uptake. Adiponectin stimulates liver gluconeogenesis (57). Adiponectin, depending on the isoform has a modulatory effect on the immune system: protein with HMW (high molecular weight) acts pro-inflammatory, whereas protein with LMW (low molecular weight) exhibits anti-inflammatory action (58). Adiponectin has antiatherogenic and protective action for endothelium, inhibits formation of macrophages and foam cells. Adiponectin stimulates angiogenesis in damaged vessels and inhibits endothelial apoptosis. What is more, it inhibits production of pro-inflammatory cytokines, *i.e.* TNF-α, interleukin-6, interleukin-10, IFNγ. Adiponectin increases nitrous oxide synthesis. It inhibits expression of some of the endothelial adhesion molecules VCAM-1, ICAM-1 and E-selectins (59).

Moreover, hypoadiponectinaemia contributes to the development of atherosclerosis, ischaemic heart disease and congestive heart failure. Adiponectin concentrations are inversely proportional to body weight, BMI, NT-proBNP, triglyceridaemia and low HDL (high-density lipoprotein) concentrations (60). Adiponectin levels are low in obese patients and have a tendency to increase when they loose weight (61). Adiponectin secretion is inhibited by proinflammatory cytokines, perhaps the inflammation may be an important factor leading to hypoadiponectinaemia in insulin-resistant and obese patients (62). In the contrary, a physical exertion increases adiponectin levels and expression of its receptors (63). Furthermore, many literature data indicate the adiponectin as a protective MetS biomarker. Bae *et al*. showed a negative correlation between MetS score and serum adiponectin levels (64). Kotani and Sakane suggested leptin:adiponectin ratio may be a marker to detect MetS (65). Adiponectin is a multifunctional protein with strong anti-inflammatory and antifibrotic properties and due to that, it can participate in the development of autoimmune diseases. Adiponectin inhibits action of cytokines, including platelet-derived growth factor (PDGF-BB) and fibroblast growth factor (66-68).

Furthermore, adiponectin is involved in pathogenesis of RA. In contrast to protective role of adiponectin in MetS, there are studies indicating on proinflammatory activity of this adipokine in joints with possible matrix degeneration (12). It increases inflammation in joints, has a proinflammatory effect on chondrocytes and contributes to destruction of cartilage (69). Adiponectin stimulates chondrocytes to produce proinflammatory cytokines: IL-6, IL-8, iNOS (70). As a matter of fact, some studies show that adiponectin may cause joint destruction in RA by activating MMP-1 and MMP-3 (71). Schäffler *et al*. in their study obtained high adiponectin levels in blood serum and synovial fluid in patients with RA compared to healthy patients (43). In another approach, Gonzalez-Gay *et al*. assessed correlation between adiponectin concentrations and cardiovascular risk factor in severe RA. In this study, the authors have found a negative correlation between adiponectin concentrations and triglicerides/HDL ratio, total cholesterol/HDL ratio and plasma glucose levels. However, BMI did not correlate with adiponectin concentrations. What is more, the authors found an independent negative correlation of high-grade inflammation (CRP levels) with circulating adiponectin concentrations in patients with severe RA (72). High-grade inflammation was independently and negatively correlated with circulating adiponectin concentrations whereas low adiponectin levels clustered with metabolic syndrome features such as dyslipidaemia and high plasma glucose levels which may indicate on contribution to atherogenesis in RA. The authors investigated RA patients treated with anti-TNF-α-antagonist (infliximab) and found that adiponectin concentrations did not change after infliximab therapy (72). In RA patients undergoing anti-TNF-α therapy, low serum adiponectin concentrations were not dependent on TNF-α but circulating adiponectin concentrations may be involved in cardiovascular risk in RA (72).

A different approach was developed by Xibillé-Friedmann *et al*. where the authors assessed whether serum adiponectin levels can predict disease activity or response to treatment with NSAIDs (non-steroidal anti-inflammatory drugs, prednisone or DMARDs (disease-modifying anti-rheumatic drugs) in RA patients at regular follow-up. Baseline adiponectin levels were not associated with clinical activity neither with therapy under NSAIDs nor DMARDs. The report showed that adiponectin can not be a predictor of therapeutic response in RA patients (22).

The role of adiponectin in AS was also investigated. Some studies report no differences between adiponectin levels among AS patients and healthy controls (73). Miranda-Filoy *et al*. in their study assessed if disease activity, systemic inflammation and metabolic syndrome were potential determinants of circulating adiponectin levels in ankylosing spondylitis (AS) patients undergoing TNF-α antagonist therapy. The presented study showed that in non-diabetic patients with AS serum adiponectin levels did not correlate with disease activity. Interestingly, in non-diabetic ankylosing spondylitis (AS) patients undergoing anti-TNF-α therapy, adiponectin concentration correlated with insulin sensitivity (47).

The role of adiponectin in SLE has not been entirely explained. Some authors demonstrated higher plasma concentrations in patients with SLE compared to healthy people (74, 75). The values of adiponectin were independent, even after reduction body mass index (74). What is more, Rovin *et al*. reported that urine adiponectin levels increased significantly with renal flare compared to renal SLE without flare, hence urine

adiponectin may be a biomarker of renal flare in SLE (75). It is worth deliberating the fact that HMW isoform of adiponectin was detected in urine of patients with acute lupus nephritis comparing to healthy individuals (75). Additionally, Chung *et al*. also reported increased plasma concentrations in SLE patients (26). These authors showed that adiponectin concentrations were negatively correlated with BMI, systolic blood pressure, dyslipidaemia and presence of MetS (26). Similarly, Sada *et al*. have reported about higher adiponectin levels in SLE patients. Furthermore, adiponectin was significantly higher in SLE patients without insulin resistance. Hence, the authors suggested that adiponectin may have an impact on insulin resistance in SLE patients (76).

Arakawa *et al*. and Masui *et al*. demonstrated lowered adiponectin expression in patients with SSc, in blood serum as well as in the affected skin. Furthermore, the authors obtained significantly lower adiponectin concentrations in diffuse type of the disease compared with patients with limited SSc (lSSc) (77, 78). Interestingly, the authors suggested correlation of decreased adiponectin level with activation of fibrotic process in the early stage of diffuse SSc (dSSc). Masui *et al*. suggested that adiponectin may be a marker of fibrosis and disease activity in SSc (78). In addition, Masui *et al*. reported lower adiponectin levels in blood serum in patients with dSSc and interstitial lung disease before cyclophosphamide treatment and, after intravenous therapy with the medication, they noted significant increase of this adipokine, especially after the first pulse (79). Tomčik *et al*. emphasised the correlation between low adiponectin levels in blood serum with skin-fold thickness in patients with SSc (80). Moreover, TGFβ (transforming growth factor β) is involved in initiation of fibrosis process in SSc. One of the endogenous anti-fibrotic mechanisms is PPARγ activity, which blocks TGFβ-dependent response (Fig. 2). Due to the strong effect of PPARγ on adiponectin gene expression, it is supposed that decreased PPARγ expression is involved in progression of skin fibrosis in patients with SSc (81). Due to anti-inflammatory properties of adiponectin it has been determined that ESR and CRP levels are negatively correlated with adiponectin levels, especially in lSSc (78). The scientists reported that due to antiatherogenic adiponectin properties the HDL cholesterol level was directly proportional to the HDL level and negatively correlated with disease duration. Therefore, longer disease duration is connected with higher cardiovascular incident risk (80).

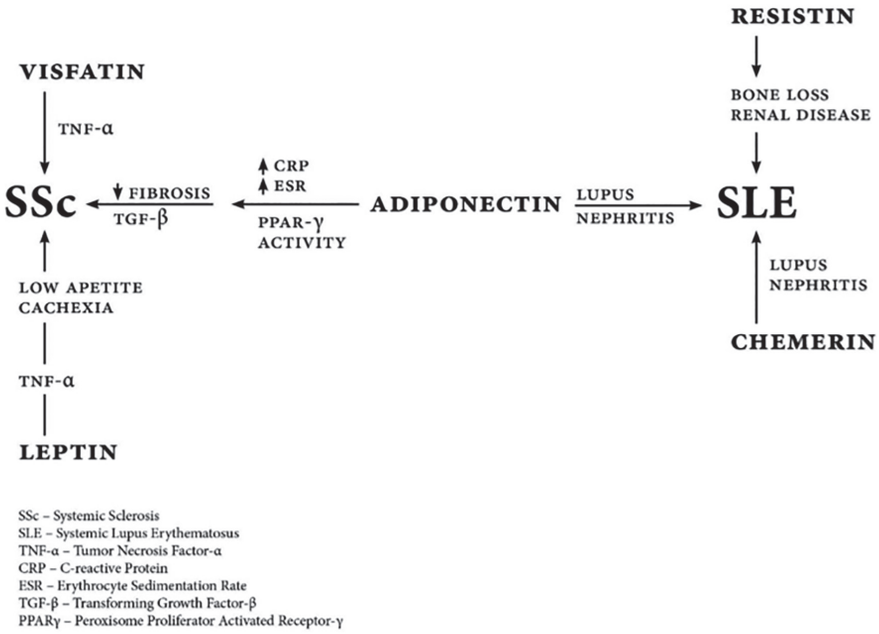


Fig. 2. Schematic representation of the biological impact of adipokines (resistin, leptin, adiponectin, visfatin and chemerin) on systemic sclerosis and systemic lupus erythematosus.

Chemerin

Chemerin is an active protein with weight 18 kDa, built of 137 amino acids. It was identified in 2003 by two independent research teams, including Medera *et al*. and Wittamer *et al*. (82, 83). Chemerin acts via the orphan G-coupled receptor chemokine-like receptor 1 (CMKLR1 or ChemR 23) and CCRL-2 (chemokine C-C motif receptor-like2). ChemR23 activation occurs through p42/44 MPK and AKT phosphorylation. This multifunctional receptor causes induction of macrophages migration, although it may play also anti-inflammatory role. CCRL-2 named also "decoy receptor", presents chemerin in close related tissues, is activated by MCP-, -2,-3, RANTES and synovial fluid of RA patients (84). Chemerin and its receptor are expressed mainly in adipose tissue (85). ChemR23 is expressed by endothelial cells, and it is upregulated by proinflammatory cytokines such as IL-1β, IL-6 and TNF-α (79).

Name chemerin originates from chimeric effect on tissues: anti-inflammatory via CMKLR1 receptor (chemokine-like receptor 1) or pro-inflammatory via ChemR23 receptor activation. Chemerin exhibits two opposite actions. On the one hand it intensifies inflammatory processes, stimulates chemotaxis of dendritic cells, macrophages and NK cells to inflammation sites. Nevertheless, on the other hand it inhibits production of inflammatory mediators and pro-inflammatory cytokines (TNF-α and Il-6) and stimulates adiponectin synthesis. Chemerin is connected with chronic inflammation and plays an important role in congenital and acquired cellular immunity (85).

Bazaoglu *et al*. described chemerin as an adipokine, which plays a role in pathogenesis of obesity in MetS. The authors reported strong correlation between chemerin serum levels with BMI, triglicerides and blood pressure in obese patients. Therefore, chemerin may be assumed as a biomarker of metabolic syndrome (86).

Intriguingly, chemerin stimulates leukocytes migration to sites of inflamma-

tion and also increases inflammatory signalling in chondrocytes, so it seems that chemerin is involved in joint inflammation (87). Chondrocytes stimulate expression both chemerin and its receptor and IL-1β increases chemerin expression (88). To support this, Berg *et al*. have demonstrated that recombinant chemerin is able to enhance the production of several proinflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8 and MMPs (MMP-1, MMP-2, MMP-3, MMP-8 and MMP-13) in human articular chondrocytes (89). These factors may develop degradation of extracellular matrix causing joint inflammation and result in irreversible destruction of cartilage in RA. Interestingly, chemerin was found in synovial fluid in RA patients and chemerin protein was found in cell supernatants of synovial fibroblasts (87). Galligan *et al*. found CCRL2 (chemokine C-C motif receptor-like2) expression on all infiltrating neutrophils and on some macrophages obtained from the synovial fluid of RA patients (90). *In vitro* studies of primary neutrophils revealed that CCRL2 messenger RNA (mRNA) was rapidly up-regulated following stimulation with lipopolysaccharide or TNF-α. Inflammatory products present in the synovial fluid activate CCLR2, supporting role of this receptor CCRL2 as a functional receptor that may be involved in the pathogenesis of RA (87).

Chemerin and ChemR23 were found in SLE skin biopsies (91). *In vitro* chemerin acts as a chemotactic factor for plasmacytoid dendritic cells (91). Vermi *et al*. suggested that chemerin is involved in migration and accumulation of plasmacytoid dendritic cells in inflamed tissues in SLE patients. Moreover, chemerin reactivity was observed in 64% of LE biopsies on endothelial cells and in the granular layer keratinocytes (92). Furthermore, De Palma *et al*. detected chemerin expression in renal tubular epithelial cells in patients with lupus nephritis (93). Further studies are required focusing on the role of chemerin in SLE.

Akamata *et al*. investigated a potential role of chemerin in the development of SSc. Increased chemerin expression in dermal blood vessels in SSc patients may be associated with the development of digital ulcers (94). In the obtained results chemerin was up-regulated in small blood vessels in SSc lesional skin, while it was down-regulated in fibroblasts surrounded with thickened collagen bundles. Chemerin is down-regulated in SSc dermal fibroblasts by autocrine TGF-β, while it is up-regulated in SSc dermal blood vessels through endothelial Fli1 deficiency. The decreased expression of chemerin was significantly reversed by TGF-β1 antisense oligonucleotide in cultured SSc dermal fibroblasts and chemerin expression was markedly decreased in dermal fibroblasts of bleomycin-treated mice. Furthermore, scientists explored a negative correlation between serum chemerin levels and estimated glomerular filtration rate in SSc patients with renal dysfunction. In SSc patients with normal renal function, patients with digital ulcers had higher serum chemerin levels than those without (94).

Visfatin

Visfatin is a 53kDa protein for the first time described in 2004 by Fukuara *et al*. (95). It is secreted by adipocytes and macrophages infiltrating the adipose tissue. Visfatin has been initially recognised as pre-B-cell colony enhancing factor (PBEF), which enhances differentiation of B-cell precursors in synergy with IL-7 and stem cell factor. On the cellular level visfatin activates insulin receptor through transductal molecules chain reactions: phosphorylation receptor substrates (insulin receptor substrate 1,2, IRS-1,2), activation of protein kinase B and mitogen-activated protein kinase (MAPK) (96). Specific visfatin receptor has not been identified yet. Visfatin has enzymatic activity, nicotinamide phosphoribosyltransferase, it participates in carbohydrate and fat metabolism. It affects lipid metabolisms via other adipokines, insulin-like growth factor (IGF), and interleukins (IL-7, IL-6, TNF-α). Moreover, visfatin stimulates monocytes to produce proinflammatory cytokines such as IL-1, IL-6 and TNF-α (97).

Visfatin is connected with development of such diseases as: atherosclerosis, metabolic syndrome, obesity, lung diseases, renal failure and some liver diseases (98). However, Olszanecka-Glinianowicz *et al*. in their study on obese women did not find any correlation between visfatin levels and metabolic syndrome. On the other hand, the authors suggested that visfatin/insulin ratio could be a good prognosing factor for development insulin resistance and MetS in obese individuals (99).

Visfatin seems to play a role as a potentially pro-inflammatory and catabolism-increasing factor in RA, even though the exact mechanism is not fully understood. For instance, visfatin stimulates the production and activity of matrix metalloproteinases (MMPs) and joint destruction in RA patients (100). Otero *et al*. demonstrated increased circulating visfatin concentrations in patients with RA compared to healthy controls (101). Results concerning visfatin levels in RA patients treated with anti-TNF-α are controversial. Most studies found decreased visfatin levels upon anti-TNF-α therapy (102, 103), while others did not show such a correlation (104). In RA non-diabetic patients undergoing anti-TNF-α therapy there was no correlation between circulating visfatin levels and clinical and laboratory parameters of disease activity or metabolic syndrome. In addition, visfatin serum levels did not change after infliximab therapy. The beneficial effect of anti-TNF-α therapy seems to be not mediated by serum vistin levels (104).

Hulejová *et al*. investigated whether visfatin plays a role in AS or not and they found out that visfatin levels did not correlate with disease activity in AS. The authors concluded that baseline levels of visfatin did not predict the change of disease activity or functional ability in patients with ankylosing spondylitis (105). Similarly, Miranda-Filloy *et al*. did not find a correlation between visfatin levels and disease duration, ESR, CRP in AS patients undergoing anti- TNF-α therapy, but visfatin concentration correlated with insulin resistance (24).

There is very little information in the literature about visfatin in SLE. Studies concerning visfatin and SLE present conflicting results. Visfatin activates human leukocytes and induces the production

of IL-1β, TNF-α, and especially IL-6 (106). Chung *et al*. stated higher levels of visfatin in SLE patients compared to controls which may reflect inflammation in SLE, although they did not correlate with metabolic or inflammatory mediators such as BMI, insulin resistance and CRP (26). On the other hand, Ozgen *et al*. investigated visfatin levels and intima-media thickness in 26 SLE patients, discovering no significant association between visfatin levels in SLE patients compared to controls (100).

Visfatin appears to be involved in the pathological process of inflammatory autoimmune diseases, including RA (101), so this adipokine may play also a pathogenetic role in SSc, but these data need evaluation. Although, previous reports did not show any correlation between visfatin levels and SSc (94), Masui *et al*. demonstrated higher serum visfatin concentrations in patients with prolonged course of diffuse SSc (107). In obtained results there was no difference in serum visfatin levels among SSc, dcSSc, lcSSc and healthy controls. However, Serum visfatin levels were significantly elevated in late-stage of dSSc (disease duration >3 years), but not in early or mid-stage dSSc compared with healthy controls, suggesting that visfatin is involved in certain pathological processes in late-stage dSSc. Furthermore, the authors hypothesise that visfatin may contribute to the resolution of skin sclerosis in late-stage dcSSc via an anti-fibrotic effect on dermal fibroblasts and Th1 polarisation of the immune response (107).

Novel adipokines

Vaspin (serpinA12) is recently discovered adipokine (108). The adipokine vaspin is mainly expressed in white adipose tissue and exhibits various beneficial effects on obesity-related processes (108). The administration of recombinant vaspin to obese mice improved glucose tolerance and insulin sensitivity, identifying this adipokine as an insulin sensitiser (108).

The risks of insulin resistance and higher risk of atherosclerosis are increased in chronic inflammatory diseases including RA (RA). Ozgen *et al*. assessed vaspin levels in patients with RA founding higher vaspin levels in RA patients compared to controls (109). Furthermore, Senolt *et al*. measured levels of vaspin in the synovial fluid of patients with RA and found that they were higher in those with osteoarthritis (110). Cantarini *et al*. were to evaluate vaspin serum levels in patients affected by juvenile idiopathic arthritis (JIA), in comparison to healthy controls, and to correlate circulating levels to parameters of disease activity. Vaspin serum level did not show statistical significant differences between JIA children with active joints and those with no active joints (111). Moreover, in contrast to in RA, vaspin level declines in active Behçet's disease, and these results suggest that different chronic inflammatory diseases exert different influences on adipokines (109).

Omentin is a 40kDa protein secreted by omental adipose tissue and it was previously identified as intelectin. It is expressed in visceral fat tissue and probably regulates insulin action (112). Obesity decreases omentin levels and its gene expression. Serum omentin levels positively correlated with plasma adiponectin levels and high-density lipoprotein and inversely correlated with waist circumference and BMI, all included in MetS (113). Interestingly, an omentin mRNA expression occured in omental adipose tissue of patients with Crohn's disease, hence omentin could be a new prognosing factor for potentially involved in chronic inflammatory diseases (114).

Omentin has a protective effect against vascular inflammation and pathological remodelling leading to atherosclerosis as well as a vasodilatory effect. In a very recent study Miura *et al*. reported about omentin in SSc patients. Serum omentin levels were significantly decreased in diffuse cutaneous SSc patients compared with limited cutaneous SSc patients, though comparable between total SSc patients and healthy controls (Table I.) In diffuse SSc, patients with a disease duration of 5 years or less had serum omentin levels significantly lower than those with a disease duration of more than 5 years. In total SSc, serum omentin levels were significantly higher in patients with elevated right ventricular systolic pressure than in the others, while serum omentin levels did not correlate with fibrotic and systemic inflammatory parameters. These results suggest that a loss of omentin-dependent protection against vascular inflammation and remodelling may be related to pathological vascular events of early diffuse SSc. The elevation of serum omentin levels may serve as a marker of vascular involvement leading to pulmonary arterial hypertension in SSc, which is possibly due to the compensatory induction of omentin against the increased pulmonary vascular tone (115).

Cantarini *et al*. assessed omentin serum levels in patients with JIA in comparison to healthy controls and parameters of disease activity. This study showed that omentin was significantly higher in JIA patients in comparison to healthy controls. In addition, the authors reported that omentin serum levels were significantly correlated with the presence and the number of active joints (111).

Apelin is a quite novel bioactive peptide that was originally identified as the endogenous ligand of the orphan G protein-coupled receptor APJ (116). This adipokine is produced mainly by adipocytes and endothelial cells (117). Apelin may act as a marker of CV risk disease due to the fact that it stimulates NO (nitric oxide) release (118). What is more, insulin upregulates the apelin expression making this adipokine attractive prognostic factor in diabetes (119). Low apelin levels have been detected in patients with high LDL levels and type 2 diabetes mellitus, both of which were associated with an increased risk for atherosclerosis (119).

It is worth emphasising the fact that, Di Franco *et al*. assessed apelin levels in early RA and found them lower than in controls. The authors suggested a potential role of apelin in pathogenesis of rheumatic diseases (120). Furthermore, scientists wanted to detect if there was a correlation between apelin levels in RA patients treated with anti-TNF-α therapy and BMI or insulin resistance. Unfortunately, no correlation was found (17).

In another study, the influence of anti-TNF-α therapy (infliximab) on apelin

Table I. The levels of particular adipokine in relevant connective tissue disease.

Adipokine	Rheumatic disease				Reference
	RA	SLE	SSc	AS	
Leptin	↑	↑	↓	ND	5, 14, 19, 21, 25-28, 30
Resistin	↑	↑	↑	ND	41-45, 47, 48, 53
Adiponectin	↑	↑	↓	ND	26, 43, 74-79
Chemerin	↑	↑	↑	ND	87, 94
Visfatin	↑	↑	↑	ND	26, 101, 107
Vaspin	↑	ND	ND	ND	109, 110
Omentin	ND	ND	↓	ND	112, 115
Apelin	↓	ND	ND	ND	120
Lipocalin-2	↑	ND	ND	ND	129

ND: no data; SLE: systemic lupus erythematosus; RA: rheumatic arthritis; SSc: systemic sclerosis; AS: ankylosing spondylitis.

levels was analysed in AS patients. A single dose of the biological drug caused a reduction of apelin levels, although this decrease was not statistical significant (121).

Lipocalin-2 (LCN-2) a 25kDA glycoprotein, also known as neutrophil gelatinase-associated lipocalin (NGAL), uterocalin, 24p3, and siderocalin (122). It is supposed that WAT is a main source of LCN-2, although it was isolated from neutrophil granules (123). What is significant, Lipocalin-2 concentrations were associated with inflammatory markers and some metabolic parameters. Yan *et al*. reported that LCN-2 was highly expressed in adipocytes and this expression was regulated by obesity inducing insulin resistance (124). In addition, hyperglycaemia, glucocorticoids and TNF-α stimulated insulin resistance, which induces the expression of Lcn-2 (125). In study of Jang *et al*. patients with MetS have higher Lcn-2 levels than those without MetS (126).

Lipocalin-2 is expressed in chondrocytes and in these cells the LCN-2 expression was regulated by leptin, adiponectin, LPS, IL-1β and dexamethasone (127). What is more, the MMP-9/Lipocalin-2 complexes have been found in patients with knee osteoarthritis, and they may be involved in matrix degeneration (128). Katano *et al*. assessing lipocalin-2 levels in synovial fluid of RA patients obtained significantly higher LCN-2 levels in patients with RA than in those with osteoarthritis (129). Furthermore, the authors reported that granulocyte macrophage colony-stimulating factor (GM-CSF) can be involved in pathogenesis of RA by upregulating LCN2 in neutrophils, followed by the induction several enzymes, such as cathepsin D, transitional endoplasmic reticulum ATPase (TERA), and transglutaminase 2 (tg2) in synoviocytes, which could stimulate proliferation of synovial cells and infiltration of inflammatory cells inside the synovium (129).

Conclusions

1. The implications between adipokines and connective tissue diseases are very complex.
2. Depending on the type of adipokine they encompass a variety of influences on metabolic status and inflammatory process in CTD.
3. One of the major adipokines, leptin, can be a predictor of disease activity in patients with RA.
4. Although anti-TNF-α therapy has a beneficial effect on disease activity in RA, it does not exert any on adipokines serum levels.
5. Further studies are needed to define the possible role of adipokines in CTD.

References

1. 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.
2. MALINOWSKI M, DEJA MA, GOŁBA KS, JANUSIEWICZ P, ROLEDER T, WOŚ S: The influence of perivascular adipose tissue on the vascular tone and function. *Kardiol Pol* 2008; 66: 317-25.
3. MACIEJEWSKA-STELMACH J, ŚLIWIŃSKA-STAŃCZYK P, ŁĄCKI JK: The role of leptin in inflammatory connective tissue diseases. *Reumatologia* 2007; 45: 219-24.
4. KARMAZYN M, PURDHAM DM, RAJAPUROHITAM V, ZEIDAN A: Signaling mechanism underlying the metabolic and other effects of adipokines on the heart. *Cardiovasc Res* 2008; 79: 279-86.
5. TIAN G, LIANG JN, WANG ZY, ZHOU D: Emerging role of leptin in rheumatoid arthritis. *Clin Exp Immunology* 2014; 177: 557-70.
6. HOWARD JK, LORD GM, MATARESE G *et al*.: Leptin protects mice from starvation-induced lymphoid atrophy and increase thymic cellularity in ob/ob mice. *J Clin Invest* 1999; 15: 1051-9.
7. FAGGIONI R, FEINGOLD KR, GRUNFELD C: Leptin regulation of the immune response and the immunodeficiency of malnutrition. *FASEB J* 2001; 15: 2565-71.
8. LAM QL, LU L: Role of leptin in immunity. *Cell Mol Immunol* 2007; 4: 1-13.
9. DE SOUZA BARBOSA V, REGO J, DA SILVA NA: Possible role of adipokines in systemic lupus erythematosus and rheumatoid arthritis. *Rev Bras Reumatol* 2012; 52: 278-87.
10. AGRAWAL S, GOLLAPUDI S, SU H, GUPTA S: Leptin activates human B cells to secrete TNF-alpha, IL-6, and IL-10 via JAK2/STAT3 and p38MAPK/ERK1/2 signaling pathway. *J Clin Immunol* 2011; 31: 472-8.
11. TARGOŃSKA-STĘPNIAK B, DRYGLEWSKA M, MAJDAN M: Adiponectin and leptin serum concentration in patients with rheumatoid arthritis. *Rheumatol Int* 2010; 30: 731-7.
12. ABELLA V, SCOTECE M, CONDE J *et al*.: Adipokines, metabolic syndrome and rheumatic diseases. *J Immunol Res* 2014; 2014: 343746.
13. YADAV A, JYOTI P, JAIN SK, BHATTACHARJEE J: Correlation of adiponectin and leptin with insulin resistance: a pilot study in healthy north Indian population. *Indian J Clin Biochem* 2011; 26: 193-6.
14. OTERO M, GOMEZ REINO JJ, GUALILLO O: Synergistic induction on nitric oxide synthase type II: *in vitro* effect of leptin and interferon-gamma in human chondrocytes and ATDC5 chondrogenic cells. *Arthritis Rheum* 2003; 48: 404-9.
15. YOSHINO T, KUSUNOKI N, TANAKA N *et al*.: Elevated serum levels of resistin, leptin, and adiponectin are associated with C-reactive protein and also other clinical conditions in rheumatoid arthritis. *Intern Med* 2011; 50: 269-75.
16. KOPEC-MEDREK M, KOTULSKA A, WIDUCHOWSKA M, ADAMCZAK M, WIECEK A, KUCHARZ EJ: Plasma leptin and neuropeptide Y concentrations in patients with rheumatoid arthritis treated with infliximab, a TNF-alpha antagonist. *Rheumatol Int* 2012; 32: 3383-9.
17. FERRAZ-AMARO I, ARCE-FRANCO M, MUNIZ J *et al*.: Systemic blockade of TNF-alpha does not improve insulin resistance in humans. *Horm Metab Res* 2011; 43: 801-8.
18. 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.

19. HÄRLE P, SARZI-PUTTINI P, CUTOLO M, STRAUB RH: No change of serum levels of leptin and adiponectin during anti-tumor necrosis factor antibody treatment with adalimumab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2006; 65: 970-1.
20. ANDERS HJ, RIHL M, HEUFELDER A, LOCH O, SCHATTENKIRCHNER M: Leptin serum levels are not correlated with disease activity in patients with rheumatoid arthritis. *Metabolism* 1999; 48: 745-8.
21. GONZALEZ-GAY MA, GARCIA-UNZUETA MT, BERJA A *et al*.: Anti-TNF-α therapy does not modulate leptin in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2009; 27: 222-8.
22. XIBILLÉ-FRIEDMANN DX, ORTIZ-PANOZO E, BUSTOS RIVERA-BAHENA C *et al*.: Leptin and adiponectin as predictors of disease activity in rheumatoid arthritis. *Clin Exp Rheumatol* 2015; 33: 471-7.
23. PARK MC, LEE SW, CHOI ST, PARK YB, LEE SK: Serum leptin levels correlate with interleukin-6 levels and disease activity in patients with ankylosing spondylitis. *Scand J Rheumatol* 2007; 36: 101-6.
24. MIRANDA-FILLOY JA, LÓPEZ-MEJIAS R, GENRE F *et al*.: Leptin and visfatin serum levels in non-diabetic ankylosing spondylitis patients undergoing TNF-α antagonist therapy. *Clin Exp Rheumatol* 2013; 31: 538-45.
25. GARCIA-GONZALEZ A, GONZALEZ LOPEZ L, VALERA-GONZALEZ IC *et al*.: Serum leptin levels in women with systemic lupus erythematosus. *Rheumatol Int* 2002; 22: 138-41.
26. CHUNG CP, LONG AG, SOLUS JF *et al*.: Adipocytokines in systemic lupus erythmetosus: relationship to inflammation, insulin resistance and coronary atherosclerosis. *Lupus* 2009; 18: 799-806.
27. VADACCA M, MARGIOTTA DC, RIGON A *et al*.: Adipokines and systemic lupus erythematosus: relationship with metabolic syndrome and cardiovascular disease risk factors. *J Rheumatol* 2009; 36: 295-7.
28. WINSZ-SZCZOTKA K, KUŹNIK-TROCHA K, KOMOSIŃSKA-VASSEV K, OLCZYK K: The serum leptin level in systemic sclerosis patients. *Ann Acad Med Siles* 2011; 65: 5-6. 42-8.
29. KOTULSKA A, KUCHARZ EJ, BRZEZIŃSKA-WCISŁO L *et al*.: A decreased serum leptin level in patients with systemic sclerosis. *Clin Rheumatol* 2001; 20: 300-2.
30. PEHLIVAN Y, ONAT AM, CEYLAN N *et al*.: Serum leptin, resistin and TNFα levels in patients with systemic sclerosis: the role of adipokines in scleroderma. *Int J Rheumatol* 2012; 15: 374-9.
31. PINA T, LOPEZ-MEJIAS R, ARMESTO S *et al*.: Relationship of leptin with adiposity and inflammation and resistin with disease severity in psoriatic patients undergoing anti-TNF-alpha therapy. J *Eur Acad Dermatol Venereol* 2015; 29: 1995-2001.
32. BARAN A, FLISIAK I, CHODYNICKA B: Role of selected adipokines in psoriasis. *Przegl Dermatol* 2011; 98: 422-8.
33. TARKOWSKI A, BJERSING J, SHESTAKOV A, BOKAREWA MI: Resistin competes with lipopolysaccharide for binding to toll-like receptor 4. *J Cell Mol Med* 2010; 14: 1419-31.
34. PANG SS, LE YY: Role of resistin in inflammation and inflammation-related diseases. *Cell Mol Immunol* 2006; 3: 29-34.
35. KARBOWSKA A, BORATYŃSKA M, KLINGER M: Resistin: A pathogenic factor or a biomarker of metabolic disorders and inflammation? *Postepy Hig Med Dosw* 2009; 63: 485-91.
36. BO S, GAMBINO R, PAGANI A *et al*.: Relationships between human serum resistin, inflammatory markers and insulin resistance. *Int J Obes* 2005; 29: 1315-20.
37. STEPPAN CM, BAILEY ST, BHAT S *et al*.: The hormone resistin links obesity to diabetes. *Nature* 2001; 409: 307-12.
38. LAZAR MA: Resistin- an obesity-associated metabolic diseases. *Horm Metab Res* 2007; 39: 710-6.
39. NORATA GD, ONGARI M, GARLASCHELLI K, RASELLI S, GRIGORE L, CATAPANO AL: Plasma resistin levels correlate with determinants of the metabolic syndrome. *Eur J Endocrinol* 2007; 156: 279-84.
40. SENOLT L, HOUSA D, VERNEROVÁ Z *et al*.: Resistin in rheumatoid arthritis synovial tissue, synovial fluid and serum. *Ann Rheum Dis* 2007; 66: 458-63.
41. BOKAREWA M, NAGAEV I, DAHLBERG L, SMITH U, TARKOWSKI A: Resistin, an adipokine with potent proinflammatory properties. *J Immunol* 2005; 174: 5789-95.
42. FORSBLAD D'ELIA H, PULLERITS R, CARLSTEN H, BOKAREWA M: Resistin in serum is associated with higher levels of IL-1Ra in post-menopausal women with rheumatoid arthritis. *Rheumatology* 2008; 47: 1082-7.
43. SCHÄFFLER A, EHLING A, NEUMANN E *et al*.: Adipocytokines in synovial fluid. *JAMA* 2003; 290: 1709-10.
44. GONZALEZ-GAY MA, GARCIA-UNZUETA MT, GONZALEZ-JUANATEY C *et al*.: Anti-TNF-alpha therapy modulates resistin in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2008; 26: 311-6.
45. KOCABAS H, KOCABAS V, BUYUKBAS S, MELIKOGLU MA, SEZER I, BUTUN B: The serum levels of resistin in ankylosing spondylitis patients: a pilot study. *Rheumatol Int* 2012; 32: 699-702.
46. SYRBE U, CALLHORF J, CONRAD K *et al*.: Serum adipokine levels in patients with ankylosing spondylitis and their relationship to clinical parameters and radiographic spinal progression. *Arthritis Rheumatol* 2015; 67: 678-85.
47. MIRANDA-FILLOY JA, LÓPEZ-MEJIAS R, GENRE F *et al*.: Adiponectin and resistin serum levels in non-diabetic ankylosing spondylitis patients undergoing TNF-α antagonist therapy. *Clin Exp Rheumatol* 2013; 31: 365-71.
48. ALMEHED K, D'ELIA HF, BOKARWA M, CARLSTEN H: Role of resistin as a marker of inflammation in systemic lupus erythematosus. *Arthritis Res Ther* 2008, 10: R15.
49. HUTCHESON J, YE Y, HAN J *et al*.: Resistin as a potential marker of renal disease in lupus nephritis. *Clin Exp Immunol* 2015; 179: 435-43.
50. HUANG Q, TAO SS, ZHANG YJ *et al*.: Serum resistin levels in patients with rheumatoid arthritis and systemic lupus erythematosus: a meta-analysis. *Clin Rheumatol* 2015; 34: 1713-20.
51. VERMA S, LI SH, WANG CH *et al*.: Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction. *Circulation* 2003; 108: 736-40.
52. OLEWICZ-GAWLIK A, DAŃCZAK-PAZDROWSKA A, KLAMA K, MACKIEWICZ S, SILNY W, HRYCAJ P: The role of adipokines in the pathogenesis of systemic sclerosis - orginal results and short literature review. *Reumatologia* 2009; 47: 329-31.
53. ADRYCH K, SMOCZYŃSKI M, ŚLEDZIŃSKI T, DETTLAFF-POKORA A, GOYKE E, ŚWIERCZYŃSKI J: Increased serum resistin concentration in patients with chronic pancreatitis: possible cause of pancreatic fibrosis. *J Clin Gastroenterol* 2009; 43: 63-8.
54. SCHERER PE, WILLIAMS S, FOGLIANO M, BALDINI G, LODISH HF: A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem* 1995; 270: 26746-9.
55. SCOTECE M, CONDE J, GÓMEZ R *et al*.: Beyond fat mass: exploring the role of adipokines in rheumatic diseases. *Scientific World Journal* 2011; 11: 1932-47.
56. LAKOTA K, WEI J, CARNS M *et al*.: Levels of adiponectin, a marker for PPAR-gamma activity, correlate with skin fibrosis in systemic sclerosis: potential utility as biomarker? *Arthritis Res Ther* 2012; 14: R102.
57. GOLA M, GRZESZCZAK W: Adiponectin-mechanism of action, the biological activity and therapeutic hopes. *Diabet Dośw Klin* 2011; 11, 2: 78-83.
58. SONG H, CHAN J, ROVIN BH: Induction of chemokine expression by adiponectin in vitro is isoform dependent. *Transl Res* 2009; 154: 18-26.
59. OUCHI N, KIHARA S, ARITA Y *et al*.: Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. *Circulation* 2001; 103: 1057-63.
60. PUSZKARSKA A, GŁUSZEK JA: Tumor necrosis factor and adiponectin in heart failure. *Choroby Serca i Naczyń* 2010; 7: 7-13.
61. OH DK, CIARALDI T, HENRY RR: Adiponectin in health and disease. *Diabetes Obes Metab* 2007; 9: 282-9.
62. 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.
63. BLÜHER M, BULLEN JW JR, LEE JH *et al*.: Circulating adiponectin and expression of adiponectin receptors in human skeletal muscle: associations with metabolic parameters and insulin resistance and regulation by physical training. *J Clin Endocrinol Metab* 2006; 91: 2310-6.
64. BAE YJ, KIM SH, CHUNG JH *et al*.: Evaluation of adiposity-related biomarkers as metabolic syndrome indicators. *Clin Nutr Res* 2013; 2: 91-9.
65. KOTANI K, SAKANE N: Leptin: adiponectin ratio and metabolic syndrome in the general Japanese population. *Korean J Lab Med* 2011; 31: 162-6.

66. ARITA Y, KIHARA S, OUCHI N *et al*.: Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle cell. *Circulation* 2012; 105: 2893-8.
67. OHASHI K, PARKER JL, OUCHI N *et al*.: Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. *J Biol Chem* 2010; 285: 6153-60.
68. FUJITA K, MAEDA M, SONODA M *et al*.: Adiponectin protects against angiotensin II-induced cardiac fibrosis trough activation of PPAR-α. Arterioscler *Thromb Vasc Biol* 2008; 28: 863-70.
69. FROMMER KW, ZIMMERMANN B, MEIER FMP *et al*.: Adiponectin-mediated changes in effector cells involved in the pathophysiology of rheumatoid arthritis. *Arthritis & Rheumatism* 2010; 62: 2886-99.
70. GÓMEZ R, SCOTECE M, CONDE J, GÓMEZ-REINO JJ, LAGO F, GUALILLO O: Adiponectin and leptin increase IL-8 production in human chondrocytes. *Ann Rheum Dis* 2011; 70: 2052-4.
71. 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.
72. GONZALEZ-GAY MA, LLORCA J, GARCIA-UZUETA MT *et al*.: High-grade inflammation, circulating adiponectin concentrations and cardiovascular risk factors in severe rheumatoid arthritis. *Clin Exp Rheumatol* 2008; 26: 596-603.
73. TOUSSIROT E, STREIT G, NGUYEN NU *et al*.: Adipose tissue, serum adipokines, and ghrelin in patients with ankylosing spondylitis. *Metabolism* 2007; 56: 1383-9.
74. DE SANCTIS JB, ZABALETA M, BIANCO NE, GARMENDIA JV, RIVAS L: Serum adipokine levels in patients with systemic lupus erythematosus. *Autoimmunity* 2009; 42: 272-4.
75. ROVIN BH, SONG H, HERBERT LA *et al*.: Plasma, urine, and renal expression of adiponectin in human systemic lupus erythematosus. *Kidney Int* 2005; 68: 1825-33.
76. SADA KE, YAMASAKI Y, MARUYAMA M *et al*.: Altered levels of adipocytokines in association with insulin resistance in patients with systemic lupus erythematosus. *J Rheumatol* 2006; 33: 1545-52.
77. ARAKAWA H, JINNIN M, MUCHEMWA FC *et al*.: Adiponectin expression is decreased in the involved skin and sera of diffuse cutaneous scleroderma patients. *Exp Dermatol* 2011; 20: 749-55.
78. MASUI Y, ASANO Y, SHIBATA S *et al*.: Serum adiponectin levels inversely correlate with the activity of progressive skin sclerosis in patients with diffuse cutaneous systemic sclerosis. *J Eur Acad Dermatol Venereol* 2012; 26: 354-60.
79. MASUI Y, ASANO Y, TAKAHASHI T *et al*.: Clinical significance of monitoring serum adiponectin levels during intravenous pulse cyclophosphamide therapy in interstitial lung disease associated with systemic sclerosis. *Mod Rheumatol* 2013; 23: 323-9.
80. TOMČIK M, ARIMA K, HULEJOVÁ H *et al*.: Adiponectin relation to skin changes and dyslipidemia in systemic sclerosis. *Cytokine* 2012; 58: 165-8.
81. WEI J, GHOSH AK, SARGENT JL *et al*.: PPARγ downregulation by TGFß in fibroblast and impaired expression and function in systemic sclerosis: a novel mechanism for progressive fibrogenesis. *PLoS One* 2010; 5: e13778.
82. MEDER W, WENDLAND M, BUSMANN A *et al*.: Characterization of human circulating TIG2 as a ligand for the orphan receptor ChemR23. *FEBS Lett* 2003; 555: 495-9.
83. WITTAMER V, FRANSSEN JD, VULCANO M *et al*.: Specific recruitment of antigen-presenting cells by chemerin, a novel processed ligand from human inflammatory fluids. *J Exp Med* 2003; 198: 977-85.
84. ZIORA K, SUWAŁA A: Chemerin-structure, biological function and link between obesity and metabolic syndrome. *Endokrynol Pediatr* 2012; 11: 49-58.
85. KAUR J, ADYA R, TAN BK, CHEN J, RANDEVA HS: Identification of chemerin receptor (ChemR23) in human endothelial cells: chemerin-induced endothelial angiogenesis. *Biochem Biophys Res Commun* 2010; 391: 1762-8.
86. BOZAOGLU K, BOLTON K, MC MILLAN J *et al*.: Chemerin is a novel adipokine associated with obesity and metabolic syndrome. *Endocrinology* 2007; 148: 4687-94.
87. EISINGER K, BAUER S, SCHÄFFLER A *et al*.: Chemerin induces CCL2 and TLR4 in synovial fibroblasts of patients with rheumatoid arthritis and osteoarthritis. *Exp Mol Pathol* 2012; 92: 90-6.
88. CONDE J, GOMEZ R, BIANCO G *et al*.: Expanding the adipokine network in cartilage: identification and regulation of novel factors in human and murine chondrocytes. *Ann Rheum Dis* 2011; 70: 551-9.
89. BERG V, SVEINBJÖRNSSON B, BENDIKSEN S, BROX J, MEKNAS K, FIGENSCHAU Y: Human articular chondrocytes express ChemR23 and chemerin; ChemR23 promotes inflammatory signalling upon binding the ligand chemerin (21-157). *Arthritis Res Ther* 2010; 12: R228.
90. GALLIGAN CL, MATSUYAMA W, MATSUKAWA A *et al*.: Up-regulated expression and activation of the orphan chemokine recptor, CCRL2, in rheumatoid arthritis. *Arthritis Rheum* 2004; 50: 1806-14.
91. CHYRA A, GAWEŁ K, CICHY J: Chemerin - a new regulator of metabolic and immune processes. *Postepy Biologii Komórki* 2011; 38: 407-21.
92. VERMI W, RIBOLDI E, WITTAMER V *et al*.: Role of ChemR23 in directing the migration of myeloid and plasmacytoid dendritic cells to lymphoid organs and inflamed skin. *J Exp Med* 2005; 201: 509-15.
93. DE PALMA G, CASTELLANO G, DEL PRETE A *et al*.: The possible role of ChemR23/Chemerin axis in the recruitment of dendritic cells in lupus nephritis. *Kidney Int* 2011; 79: 1228-35.
94. AKAMATA K, ASANO Y, TANIGUCHI T *et al*.: Increased expression of chemerin in endothelial cells due to Fli1 deficiency may contribute to the development of digital ulcers in systemic sclerosis. *Rheumatology* 2015; 54: 1308-16.
95. FUKUHARA A, MATSUDA M, NISHIZAWA M *et al*.: Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. *Science* 2005; 307: 426-30.
96. FOREMSKA-ICIEK J, PUPEK-MUSIALIK D: The assessment of correlations between selected adipokines concentrations, biochemical and anthropometric parameters and glomerular filtration in patients with metabolic syndrome. *Medical News* 2011; 80: 241-9.
97. MOSCHEN AR, KASER A, ENRICH B *et al*.: Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. *J Immunol* 2007; 178: 1748-58.
98. JASIŃSKA A, PIETRUCZUK M: Adipocytokines–proteins of multidirectional function. *J Lab Diagn* 2010; 46: 331-8.
99. OLSZANECKA-GLINIANOWICZ M, KOCEŁAK P, NYLEC M, CHUDEK J, ZAHORSKA-MARKIEWICZ B: Circulating visfatin level and visfatin/insulin ratio in obese women with metabolic syndrome. *Arch Med Sci* 2012; 8: 214-8.
100. OZGEN M, KOCA SS, AKSOY K, DAGLI N, USTUNDAG B, ISIK A: Visfatin levels and intima-media thickness in rheumatic diseases. *Clin Rheumatol* 2011; 30: 757-63.
101. OTERO M, LOGO 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.
102. SENOLT L, KRYŠTŮFKOVÁ O, HULEJOVÁ H *et al*.: The level of serum visfatin (PBEF) is associated with total number of B cells in patients with rheumatoid arthritis and decreases following B cell depletion therapy. *Cytokine* 2011; 55: 116-21.
103. KLAASEN R, HERENIUS MM, WIJBRANDTS CA *et al*.: Treatment-specific changes in circulating adipocytokines: a comparison between tumor necrosis factor blockade and glucocorticoid treatment for rheumatoid arthritis. *Ann Rheum Dis* 2012; 71: 1510-6.
104. GONZALEZ-GAY MA, VAZQUEZ-RODRIGUEZ TR, GARCIA-UNZUETA MT *et al*.: Visfatin is not associated with inflammation or metabolic syndrome in patients with severe rheumatoid arthritis undergoing anti-TNF-alpha therapy. *Clin Exp Rheumatol* 2010; 28: 56-62.
105. HULEJOVÁ H, LEVITOVÁ A, KUKLOVÁ M *et al*.: No effect of physiotherapy on the serum levels of adipocytokines in patients with ankylosing spondylitis. *Clin Rheumatol* 2012; 31: 67-71.
106. MOSCHEN AR, KASER A, ENRICH B *et al*.: Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. *J Immunol* 2007; 178: 1748-58.
107. MASUI Y, ASANO Y, SHIBATA S *et al*.: A possible contribution of visfatin to the resolution of skin sclerosis in patients with diffuse cutaneous systemic sclerosis via a direct anti-fibrotic effect on dermal fibroblasts and Th1 polarization of the immune response. *Rheumatology* 2013: 52:1239-44.
108. HIDA K, WADA J, EGUCHI J *et al*.: Visceral

adipose tissue-derived serine protease inhibitor: a unique insulin-sensitizing adipocytokine in obesity. *Proc Natl Acad Sci* 2005; 102: 10610-5.

109. OZGEN M, KOCA SS, DAGLI N, BALIN M, USTUNDAG B, ISIK A: Serum adiponectin and vaspin levels in rheumatoid arthritis. *Arch Med Res* 2010; 41: 457-63.
110. SENOLT L, POLAŃSKA M, FILKOVÁ M *et al*.: Vaspin and omentin: new adipokines differentially regulated at the site of inflammation in rheumatoid arthritis. *Ann Rheum Dis* 2010; 69: 1410-1.
111. CANTARINI L, SIMONINI G, FIORAVANTI A *et al*.: Circulating levels of the adipokines vaspin and omentin in patients with juvenile idiopathic arthritis, and relation to disease activity. *Clin Exp Rheumatol* 2011; 29: 1044-8.
112. YANG RZ, LEE MJ, HU H *et al*.: Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. *Am J Physiol Endocrinol Metab* 2006; 290: E1253-61.
113. DE SOUZA BATISTA CM, YANG RZ, LEE MJ *et al*.: Omentin plasma levels and gene expression are decreased in obesity. *Diabetes* 2007; 56: 1655-61.
114. SCHAFFLER A, NEUMEIER M, HERFARTH H, FURST A, SCHOLMERICH J, BUCHLER C: Genomic structure of human omentin, a new adipocytokine expressed in omental adipose tissue. *Biochim Biophys Acta* 2005; 1732: 96-102.
115. MIURA S, ASANO Y, SAIGUSA R *et al*.: Serum omentin levels: A possible contribution to vascular involvement in patients with systemic sclerosis. *J Dermatol* 2015; 42: 461-6.
116. TATEMOTO K, HOSOYA M, HABATA Y *et al*.: Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. *Biochem Biophys Res Commun* 1998; 251: 471-6.
117. KIDOYA H, TAKAKURA N: Biology of the apelin-APJ axis in vascular formation. *J Biochem* 2012; 152: 125-31.
118. JAPP AG, CRUDEN NL, AMER DA *et al*.: Vascular effects of apelin *in vivo* in man. *J Am Coll Cardiol* 2008; 52: 908-13.
119. TASCI I, DOGRU T, NAHARCI I *et al*.: Plasma apelin is lower in patients with elevated LDL-cholesterol. *Exp Clin Endocrinol Diabetes* 2007; 115: 428-32.
120. DI FRANCO M, SPINELLI FR, METERE A *et al*.: Serum levels of asymmetric dimethylarginine and apelin as potential markers of vascular endothelial dysfunction in early rheumatoid arthritis. *Mediators Inflamm* 2012; 2012: 347268.
121. GENRE F, MIRANDA-FILLOY JA, LÓPEZ-MEJIAS R *et al*.: Apelin serum levels in non-diabetic ankylosing spondylitis patients undergoing TNF-α antagonist therapy. *Clin Exp Rheumatol* 2013; 31: 532-7.
122. FLOWER DR: The lipocalin protein family: structure and function. *Biochem J* 1996; 318: 1-14.
123. TRIEBEL S, BLASER J, REINKE H, TSCHESCHE H: A 25 kDa alpha 2-microglobulin-related protein is a component of the 125 kDa form of human gelatinase. *FEBS Lett* 314: 386-8.
124. YAN QW, YANG Q, MODY N *et al*.: The adipokine lipocalin-2 is regulated by obesity and promotes insulin resistance. *Diabetes* 2007; 56: 2533-40.
125. LIN Y, BERG AH, IYENGAR P *et al*.: The hyperglicemia-induced inflammatory response in adipocytes: the role of reactive oxygen species. *J Biol Chem* 2005; 280: 4617-26.
126. JANG Y, LEE JH, WANG Y, SWEENEY G: Emerging clinical and experimental evidence for the role of lipocalin-2 in metabolic syndrome. *Clin Exp Pharmacol Physiol* 2012; 39: 194-9.
127. OWEN HC, ROBERTS SJ, AHMED SF, FARQUHARSON C: Dexamethasone-induced expression of the glucocorticoid response gene lipocalin 2 in chondrocytes. *Am J Physiol Endocrinol Metab* 2008; 294: E1023-34
128. GUPTA K, SHUKLA M, COWLAND JB, MALEMUD CJ, HAQQI TM: Neutrophil gelatinase-associated lipocalin is expressed in osteoarthritis and forms a complex with matrix metalloproteinase 9. *Arthritis Rheum* 2007; 56: 3326-35.
129. KATANO M, OKAMOTO K, ARITO M *et al*.: Implication of granulocyte-macrophage colony-stimulating factor induced neutrophil gelatinase- associated lipocalin in pathogenesis of rheumatoid arthritis revealed by proteome analysis. *Arthritis Res Ther* 2009; 11: R3.