Adiponectin and leptin serum concentrations in patients with rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease, which affects predominantly synovial joints, causing irreversible joint destruction. Although RA is considered to be a non-fatal disease, higher overall mortality is associated with the disease. Life expectancy in RA patients (pts) is reduced by an average of 3 to 18 years in comparison with non RA population [1, 2]. One of the most frequent causes of death is cardiovascular disease (CVD), due to the development of premature, accelerated atherosclerosis [1, 2, 3]. Obesity is an established risk factor for coronary artery disease (CAD) and increased mortality in the general population. However, chronic RA inflammation is accompanied by loss of body cell mass (BCM), defined as rheumatoid cachexia [1]. White adipose tissue (WAT) is the main energy store of the body, involved in regulation of energy homeostasis and metabolism. WAT is also currently considered a highly active endocrine organ, that produces a number of biologically active molecules, called adipokines [4, 5, 6]. More than 50 adipokines have been identified up till now: chemokines, cytokines [tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-8, IL-10], complement system proteins, proteins involved in hemostasis, glucose homeostasis (adiponectin, resistin), lipid metabolism, angiogenesis and appetite regulation (leptin) [4, 7].

Adiponectin is a protein, mainly produced by adipocytes and abundantly present in the circulation, accounting for 0,01% of total plasma protein. It is associated with glucose and

lipid metabolism. Adiponectin exerts anti-inflammatory action, which results from the reduction of secrection and activity of TNF-α and IL-6, as well as induction of Il-10 and IL-1 receptor antagonist (IL-1Ra) [4]. Decreased adiponectin levels in hypertensive pts are correlated with endothelial dysfunction, which represents the earliest stage of atherosclerosis. Higher adiponectin levels are linked with a lower risk of myocardial infarction [8].

Leptin is a peptide, produced mainly by WAT cells and its circulating levels are directly correlated with WAT mass. The main role of leptin is the regulation of body weight by inhibiting food intake and stimulation of energy expenditure at the hypothalamic level [9]. Leptin levels increase during infection and inflammation, as a result of enhanced production, mediated by pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). Leptin induces neutrophil chemotaxis, activates monocytes and macrophages, enhancing their phagocytic activity. It also regulates T-cell proliferation and acivity, driving T-cell differentiation toward Th_1 response, accounting for pro-inflammatory activity [9, 10]. On the other hand, it has been reported, that leptin may also stimulate production of anti-inflammatory cytokines by monocytes and macrophages [11].

Conflicting data on adipokines' role in RA have been reported. Leptin concentrations were found to be similar [12, 13, 14, 15, 16], lower [17], or higher [18, 19] in comparison with healthy controls or with pts with osteoarthritis (OA) [20]. Plasma levels of adiponectin, leptin and visfatin were found to be increased in RA pts [21] or did not differ significantly in RA pts and in healthy controls [22].

The aim of the study was to investigate adiponectin and leptin concentrations in a group of RA pts in relation with different disease duration and activity.

Materials and methods

The study group consisted of 80 consecutive RA pts treated in the Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin. All patients

fulfilled the American College of Rheumatology criteria for RA diagnosis [23]. Informed consent was obtained from the patients according to the Declaration of Helsinki. The Ethical Committee of the Medical University of Lublin approved the design of the study.

Patients' charts were reviewed for demographic information, clinical diagnosis, radiographic information. Erosive form of RA was diagnosed in those pts who presented erosions on joint surfaces of bones in radiograms of hands and/or feet, according to Steinbrocker et al.'s criteria [24]. Extraarticular symptoms observed in the pts included: rheumatoid nodules, amyloidosis, sicca syndrome, interstitial lung disease. Disease activity was determined using the 28 joints Disease Activity Score (DAS28), calculated with the number of swollen and tender joints, patient's global assessment of disease activity and erythrocyte sedimentation rate (ESR).

Routine laboratory data were determined in all patients: C-reactive protein (CRP), ESR, creatinine, hemoglobin (Hb), erythrocyte (ERY) and platelet (PLT) count. Modification of diet in renal diseases (MDRD) was calculated for every patient to estimate the glomerular filtration rate (GFR) using serum creatinine concentration and demographic factors [25]. Serum level of CRP was measured by immunoturbidimetric assay, with the upper limit of the normal range at 5 mg/l. Total cholesterol (TC), high-density lipoproteins (HDL) cholesterol, triglycerides (TG) were also measured using the standard enzymatic technique (BIOMAXIMA). Low density lipoproteins (LDL) cholesterol was calculated according to the Friedewald formula. Assessment of nutritional status markers [serum albumin, body mass index (BMI), tricipital skin fold (TSF)] was performed. Serum albumin was measured by photometric test with bromocresol green (normal range 3,8- 5,1 g/dl). TSF was measured in both upper limbs, in the mid-point between acromion and olecranon with a Harpenden calliper. The mean of these two measures was calculated for every patient. Although a long disease duration was noticed in half of our pts, the signs of malnutrition syndrome (BMI < 20 kg/m^2 and albumin level <3 g/dl) were observed only in one female patient.

Serum samples were obtained and stored at -80^0 C. Adiponectin was determined by a commercial enzyme-linked immunosorbent assay (ELISA) (Human Adiponectin Quantikine, R&D, Germany). The normal range of serum adiponectin according to manufacturer's data was between 0,87 and 21,4 ug/ml (mean 6,64); the mean detection limit was 0,246 ng/ml. Leptin was determined by a commercial enzyme-linked immunosorbent assay (ELISA) (Human Leptin Quantikine, R&D, Germany). The normal range of serum leptin according to manufacturer's data was in women between 3,88 and 77,27 ng/ml (mean 20,68); in men between 2,21 and 11,15 ng/ml (mean 4,76); detection limit 7,8 pg/ml.

Statistics. Correlation between quantitative variables was assessed by Spearman's correlation coefficients. In order to compare subgroups of patients, Student's test or non-parametric Mann-Whitney *U* test, respectively, were used. For all tests, *P* values less or equal to 0,05 were considered significant.

Results.

Demographic and disease-related variables

Table I presents the basic characteristics of the study group. The mean number of tender joints was 9,61 (7,2) (range 0- 28), the mean number of swollen joints was 7,1 (5,1) (range 0- 19). The mean patient's global assessment of disease activity (visual analogue scale 0- 100 mm) was 52,9 (24,1) (range 0- 93). High disease activity (DAS28 > 5,1) was noted in 50 pts (62,5%) (47 women and 3 men) and moderate or low disease activity (DAS28 ≤ 5,1) in 30 pts (37,5%) (25 women and 5 men). Table II presents differences between pts with long-standing RA (disease duration > 10 years) and with shorter disease duration (≤ 10 years).

All the patients were treated in the past with at least 1 disease modifying antirheumatic drug (DMARD) which included: methotrexate (MTX), leflunomide (LEF), sulphasalazine (SS), chloroquine (HQ), intramuscular gold salts (GS), cyclosporin A (CYA), cyclophosphamide (CYC). At the time of evaluation 77 pts were treated with DMARDs: MTX (27 pts, 35,1%),

LEF (23 pts, 29,9%), SS (5 pts, 6,5%), HQ (3 pts, 3,9%), CYA (2 pts, 2,6%), CYC (2 pts, 2,6%), combination of MTX and LEF (7 pts, 9,1%), MTX and CYA (4 pts, 5,2%), MTX and Infliximabe (3 pts, 3,9%), MTX and Etanercept (1 pts, 1,3%). In 47 pts (58,8%) low-dose prednisone (5- 10 mg/day) was used in the treatment.

Serum adiponectin concentration

The mean (SD) adiponectin serum concentration in all the pts was 15,2 (9,4) ug/ml (range 2,95- 58,89) and maintained within the normal range. Adiponectin levels did not differ significantly in women and in men [15,5 (9,6) ug/ml vs 11,4 (7,9) ug/ml]. There were no correlations between adiponectin and BMI as well as TSF.

In pts with long-standing RA adiponectin levels were significantly higher than in pts with disease duration <10 years [17,7 (11,3) ug/ml (range 2,95- 58,9) vs 12,7 (6,4) ug/ml (range 4,0- 31,1) (p=0,047) (Fig. 1)]. Serum adiponectin levels correlated positively both with the age of pts (r_S=0,32, p=0,003) and the disease duration (r_S=0,38, p=0,0006) (Tabb. III). There was a significant negative correlation between adiponectin concentration and MDRD GFR (r_S=- 0,23, p=0,04) (Tab. III).

A negative correlation was found between adiponectin level and the number of swollen joints (r_S= -0,26, p=0,02). There was also a strong positive correlation between serum adiponectin and HDL-cholesterol (r_S=0,40, p=0,0003) (Tab. III).

Serum leptin concentration

The mean (SD) leptin serum concentration was higher in women 11,13 (9,8) ng/ml (range 0,9- 47,6) than in men 3,6 (5,6) ng/ml (range 0,5- 17,5) and the difference was statistically significant (p=0,001). Mean leptin concentrations in our pts remained within normal ranges according to manufacturer's data. Leptin level was above normal range in 1 male patient due to high BMI (30,3 kg/m^2). Leptin levels below normal range were observed in 23 pts (18 women and 5 men) and were associated with BMI < 20 kg/m^2 in 8 pts (7 women and 1 man).

Leptin concentrations correlated positively with BMI both in women (r_S=0,58, p=0,0001) and in men (r_S= 0,94, p=0,002). There was a positive correlation between leptin levels and TSF (r_S= 0,59, p=0,0001) (Tab. III).

A borderline, negative correlation was observed between leptin concentration and MDRD GFR (r_S= -0,22, p=0,05))Tab. III).

There were positive correlations between serum leptin levels and TC levels (r_S= 0,32, p=0,004) and between leptin and LDL-cholesterol levels (r_S= 0,34, p= 0,003) (Tab. III).

Adipokines serum concentrations in pts with long long-standing RA

When assessing pts with long-standing RA we found negative correlations between adiponectin levels and markers of disease activity: number of tender joints (r_S= -0,38, p= 0,02), number of swollen joints (r_S= -0,45, p= 0,003) and a borderline correlation with DAS28 (r_S= -0,31, p= 0,05) (Tab. III).

Stepwise multiple regression analysis demonstrated a positive relationship between DAS28 value and leptin level in pts with long-standing RA (R^2= 0,158, p=0,01).

Discussion

In the presented group of RA pts, the mean serum concentrations of adiponectin and leptin remained within normal ranges. However, adipokines' levels were changing in the course of the disease. Adiponectin concentration was significantly higher in the group of pts with long-standing RA in comparison with pts with disease duration < 10 years. That relationship was noted in spite of comparable inflammatory disease activity in both groups. It was observed, that adiponectin concentration significantly increased in relation with the increasing age of pts and disease duration. Additionally, there was a correlation between adiponectin concentration and the value of MDRD GFR, which is a good indicator of renal function, much better than serum creatinine concentration or creatinine clearance [25]. The observation indicates, that increasing adiponectin level might be associated with progressive reduction of glomerular filtration rate in the course of the disease.

Our results support the idea, that adipokines influence the inflammatory process activity in the course of RA. Negative correlations between adiponectin concentrations and symptoms of joint disease activity (number of tender and swollen joints, DAS28 value) contribute to the anti-inflammatory adiponectin function. In contrast, leptin concentration was positively related to DAS28 value, which may be connected with the proinflammatory leptin role.

There were also significant correlations between concentrations of adipokines and lipid profile components. It was observed, that the increased adiponectin level was associated with increased HDL-cholesterol, whereas increased leptin level was related to increased TC and LDL-cholesterol levels. The observation suggests a protective metabolic function of adiponectin and proatherogenic leptin role.

Consistently with reports in literature, in our group of pts leptin levels were significantly higher in women than in men and correlated positively with markers of nutritional status (BMI and TSF). TSF is an objective parameter of nutritional status and gives information about fat mass exclusively [26].

According to the literature, leptin levels are higher in women than in men. Circulating leptin levels are directly correlated with WAT mass and BMI [4, 12, 20]. We did not find a relationship between adiponectin and BMI or TSF, similarly to the previous reports [27, 28]. Nakatani et al. reported, that in Japanese adults adiponectin levels correlated negatively with BMI, TC, TG and positively with HDL-cholesterol [29]. We found no reports on relationship between adipokines and lipid profile changes in RA pts.

Increasing number of reports describing differential and conflicting results, have been presented in literature on adipokines' role in inflammatory diseases and in RA.

The evidence shows, that leptin acts as a pro-inflammatory cytokine. From a structural point of view leptin belongs to the type 1 cytokine superfamily. It may be produced not only by adipocytes, but also by inflammatory cells. Different inflammatory stimuli (TNF-α, IL-1, IL-

6, lipopolysaccharide) regulate leptin mRNA expression and circulating levels, suggesting that short-time release of stored leptin is associated with acute inflammation. Leptin induces T-cell activation and modifies T-cell differentiation towards Th_1 response, connected with pro-inflammatory function [30]. In chronic inflammation prolonged stimulation induces a supression of leptin synthesis [12, 30].

In RA pts leptin concentrations were found to be similar to those of healthy controls [13, 14, 15, 16] and pts with osteoarthritis (OA) [20]. No correlation was reported between serum leptin levels and disease stages or disease activity, defined with the value of ESR, CRP [14, 16], DAS [13, 20] or presence of joint erosions [16]. In contrast, Popa et al reported that in RA pts plasma leptin concentration was inversely correlated with markers of inflammation (Il-6, CRP), suggesting, that long term stimulation of WAT by pro-inflmmatory cytokines inhibits leptin production [15]. Lee et al. reported significantly higher serum leptin levels in RA pts with high disease activity, as well as positive correlations between leptin and DAS28, CRP values [31]. In other publications, leptin levels were reported to be significantly higher in RA pts than in control subjects [18, 19, 21, 32], significantly correlated with CRP [21] or had no correlation with clinical and laboratory parameters of disease activity [32]. Bokarewa et al found that leptin plasma concentrations were higher than in synovial fluid samples obtained simultaneously. Decreased leptin level in synovial fluid was associated with non-erosive joint disease, suggesting a protective leptin effect against RA destruction [18].

Earlier, when assessing the group of 37 RA pts, we found that leptin concentrations were significantly higher in pts with erosive joint disease than in pts without erosions. In pts with long-standing RA leptin levels correlated positively with value of DAS28, ESR and number of tender joints. There was also a tendency of correlation between leptin level and cystatin C concentration (novel renal function parameter). The results suggested, that leptin levels were increased in pts with higher disease activity and the risk of progressive joint destruction [12].

In the present study we confirmed the observation of proinflammatory leptin function in the course of RA. Additional observation on the metabolic role of leptin were also performed.

Many reports have been published in the field of endocrinology and CVD, dealing with the protective metabolic role of adiponectin (anti-diabetic, anti-atherogenic), although little is known on the adiponectin function in inflammatory diseases, such as RA.

Adiponectin itself reduces the release of pro-inflammatory cytokines and increases production of ant-inflammatory ones from activated inflammatory cells. Pro-inflammatory cytokines (TNF-α, IL-6) suppress adiponectin production and thus an inverse correlation has been noted between adiponectin concentration and markers of inflammation (CRP, IL-6) [33]. Chronic inflammation associated with obesity, diabetes, atherosclerosis and CVD is characterized by decreased adiponectin level [33]. Recently there has been a growing interest in adiponectin role in pts with CHF. High plasma levels of adiponectin observed in pts with established CHF were associated with poor prognosis and mortality. Reduced renal clearance could account for higher adiponectin concentration in CHF pts [34]. In haemodialysis pts low plasma adiponectin levels were associated with pre-existing CVD and predicted mortality outcomes [35].

Some reports suggest, that in joint diseases adiponectin might exert pro-inflammatory effects. Adiponectin can induce the cultured synovial fibroblasts to release mediators of joint destruction: Il-6 and metalloproteinase-1 (MMP-1), but not TNF-α and IL-1β [36]. High concentrations of adiponectin were observed in synovial fluid of RA pts with synovial fibroblasts distinctly rich in adiponectin [37]. In contrast, Lee et al. observed, that adiponectin significantly mitigated the severity of arthritis in collagen-induced arthritis in mice, with decreased expression of TNF-α, IL-1β, MMP-3 in RA synovial fibroblasts. These data suggest an anti-inflammatory adiponectin role in the pathophysiology of RA [38].

In clinical observations, it was reported, that adiponectin plasma levels of RA pts did not differ significantly [21] or were markedly increased in comparison with healthy controls [21, 27]. No correlation was found between adiponectin and systemic inflammatory markers (CRP, ESR) [27] or a positive correlation with CRP was noted [21]. Increased adiponectin concentrations were observed in synovial fluid of RA in comparison with OA pts, which suggests a pro-inflammatory role in arthritis [27, 39]. Serum adiponectin levels were higher than those in synovial fluid, indicating, that peripheral fat stores are major producers of serum adiponectin [27].

Recent reports in literature demonstrate, that anti-TNF treatment was associated with an increase [8, 22, 28, 39] or no change in adiponectin levels [40]. The adiponectin levels were positively correlated with the endothelium-dependent vasodilatation and negatively with DAS28 [8]. Other reports demonstrated no correlation between adiponectin and clinical backgrounds or markers of disease activity after anti-TNF treatment [28, 41].

Conclusions

Although adiponectin and leptin concentrations remained within normal ranges in RA pts, a significant increase of adiponectin level was observed in relation to the age and disease duration. That might be connected with decreased GFR in older pts. Significant correlations between adipokines' concentrations and lipid profile components confirm their involvement in the process of atherosclerosis: protective adiponectin effect and proatherogenic leptin function. In pts with long-standing RA adipokines' concentrations were significantly associated with the joints disease activity, indicating anti-inflammatory adiponectin and proinflammatory leptin role.

List of abreviations

Rheumatoid arthritis (RA), cardiovascular disease (CVD), coronary artery disease (CAD), chronic heart failure (CHF), osteoarthritis (OA), body cell mass (BCM), disease activity 28 joints score (DAS28), body mass index (BMI), tricipital skin fold (TSF), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), metalloproteinase-1 (MMP-1), white adipose tissue (WAT).

The authors declare that they have no competing interests.

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Figure 1. Serum adiponetin levels in pts with RA of duration < 10 years and >10 years (p=0,047).

Table I. Basic characteristics of 80 RA pts

Variable	**Value**
Gender (F/M)	72 (90%)/ 8(10%)
Age (years)	53,7 (13,1) (range 19- 89)
Disease duration (months)	131,9 (93,7) (range 3- 420)
Long-standing RA (> 10 years)	40 (50 %)
Erosive RA	59 (73,8%)
Extra-articular symptoms	39 (48,8%)
RF positivity	52 (65 %)
ESR (mm/h)	44,6 (26,1) (range 9- 125)
CRP (mg/l)	29,5 (28,6) (range 1,0- 110,7)
DAS28 (0- 10)	5,54 (1,4) (range 2,1- 8,4)
Serum albumin (g/dl)	3,86 (0,6) (range 1,9- 5,0)
Hemoglobin (g/dl)	12,01 (1,3) (range 9,0- 15,2)
BMI (kg/m^2)	25,2 (4,4) (range 17,0- 36,9)
TSF (mm)	20,2 (7,7) (range 5,5- 41,0)
Creatinine (mg/dl)	0,84 (0,2) (range 0,6- 1,6)
MDRD GFR ($ml/min/1,73\ m^2$)	81,1 (17,4) (range 34- 113)

Values are: mean (SD) or n (%)

Table II. Characteristics of pts with disease duration ≤ 10 years and > 10 years.

Variable	**RA duration ≤ 10 years**	**RA duration >10 years**	**p**
Gender (F/M)	35 (87,5%)/ 5(12,5%)	37 (92,5%)/ 3(7,5%)	NS
Age (years)	50,4 (12,3)	56,9 (13,2)	*0,02

Disease duration (months)	62,4 (38,3)	201,5 (79,8)	*<0,001
Erosive RA	22 (55%)	37 (92,5%)	*0,004
Extra-articular symptoms	16 (40%)	23 (57,5%)	NS
RF positivity	23 (57,5 %)	29 (72,5%)	NS
High disease activity (DAS28>5,1)	24 (60%)	26 (65%)	NS
ESR (mm/h)	44,8 (28,8)	44,4 (23,5)	NS
CRP (mg/l)	30,0 (26,4)	29,1 (30,9)	NS
DAS28 (0- 10)	5,52 (1,5)	5,6 (1,4)	NS
Hemoglobin (g/dl)	11,8 (1,6)	12,1 (1,2)	NS
TC (mg/dl)	201,7 (45,6)	223,7 (60,9)	NS
HDL-cholestrol (mg/dl)	56,5 (12,1)	62,1 (17,9)	NS
LDL-cholesterol (mg/dl)	119,7 (35,5)	130,5 (46,7)	NS
TG (mg/dl)	135,0 (61,9)	137,4 (59,3)	NS
Serum albumin (g/dl)	3,83 (0,5)	3,88 (0,6)	NS
BMI (kg/m^2)	25,0 (4,4)	25,4 (4,4)	NS
TSF (mm)	20,4 (7,6)	20,02 (7,9)	NS
Creatinine (mg/dl)	0,86 (0,2)	0,83 (0,2)	NS
MDRD GFR (ml/min/1,73 m^2)	80,7 (18,6)	81,5 (16,6)	NS
Adiponectin (ug/ml)	12,7 (6,4)	17,7 (11,2)	*0,02
Leptin (ng/ml)	11,2 (11,9)	9,5 (7,1)	NS

Values are: mean (SD) or n (%)

Table III. Correlations between serum adiponectin, leptin levels and parameters in RA pts.

Variable	**Adiponectin**	**Leptin**
The group of 80 RA pts		
Age	r= 0,32 (p=0,003)	NS
Disease duration	r= 0,38 (p=0,0006)	NS
BMI	NS	F: r= 0,58 (p=0,0001) M: r= 0,94 (p=0,002)
TSF	NS	r= 0,59 (p=0,0001)
MDRD GFR	r= -0,23 (p=0,04)	r= -0,22 (p=0,05)

Total cholestrol	NS	r= 0,32 (p=0,004)
HDL-cholestrol	r= 0,40 (p=0,0003)	NS
LDL-cholesterol	NS	r= 0,34 (p=0,003)
The group of 40 pts with long-standing RA (> 10 years)		
Tender joints count	r= -0,38 (p=0,02)	NS
Swollen joints count	r= -0,45 (p=0,003)	NS
DAS28	r= -0,31 (p=0,05)	NS

r- Spearman correlation, NS- not significant, F- female, M- male

Figure 1. Serum adiponetin levels in pts with RA of duration < 10 years and >10 years (p=0,047).