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Serum adiponectin in rheumatoid arthritis and osteoarthritis

Adiponektyna w surowicy w reumatoidalnym zapaleniu stawów i chorobie zwyrodnieniowej stawów

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Słowa kluczowe: adiponektyna, BMD, reumatoidalne zapalenie stawów, choroba zwyrodnieniowa stawów.

Summary

Adiponectin belongs to the family of adipokines, the proteins produced by the white adipose tissue, which is presently considered as an active secretion organ. Adiponectin exerts a protective effect on blood vessels and is claimed to play a preventive role in obesity. Adiponectin's function in inflammation and rheumatic disorders has not been clarified to date, but the protein is considered an important inflammatory modulator. In this study we assessed serum adiponectin levels in rheumatoid arthritis (RA) and osteoarthritis (OA) patients and found a correlation between serum adiponectin level and other markers as well as bone mass density changes, activity of disease, disease duration and the age of the patients. The blood was collected from 44 RA and 42 OA patients who constituted the control group. The serum level of adiponectin in RA and OA patients ranged respectively from 2.6 to 50 μg/ml (median 14.91) and 4.6 to 39.64 μg/ml (median 10.07). No differences in adiponectin concentrations were noted between RA and OA patients, nor between subsets of different age or body mass in both groups. A negative correlation between adiponectin concentrations and body mineral density (BMD) was found in both RA ($r = –0.35$; $p < 0.05$) and OA groups ($r = –0.42$; $p < 0.05$). In osteoarthritis higher adiponectin concentrations were noted in longer-lasting disease ($r = 0.43$; $p < 0.05$).

Streszczenie

Adiponektyna należy do rodziny adipokin, białek produkowanych przez białą tkankę tłuszczową. Adiponektyna wywiera protekcyjny wpływ na naczynia krwionośne i odgrywa profilaktyczną rolę w otyłości. Funkcja adiponektyny w zapaleniu i schorzeniach reumatoidalnych nie jest wyjaśniona, ale białko to prawdopodobnie jest ważnym modulatorem zapalenia. W pracy oceniano stężenie adiponektyny w surowicy u 44 chorych na reumatoidalne zapalenie stawów (RZS) i 42 z chorobą zwyrodnieniową stawów (ChZS). Poszukiwano korelacji z innymi markerami, gęstością mineralną kości, czasem trwania choroby i wiekiem pacjentów. Stężenie adiponektyny w surowicy u chorych na RZS i ChZS wynosiło odpowiednio od 2,6 do 50 μg/ml (średnio 14,91) i 4,6–39,64 μg/ml (średnio 10,07). Nie stwierdzono różnic znamiennych statystycznie w stężeniu adiponektyny pomiędzy grupami. Ujemną korelację zaobserwowano pomiędzy stężeniem adiponektyny a BMD w grupie chorych na RZS ($r = –0,35$; $p < 0,05$) i ChZS ($r = –0,42$; $p < 0,05$). W ChZS wyższe stężenia adiponektyny stwierdzono u tych chorych, u których choroba miała dłuższy przebieg ($r = 0,43$; $p < 0,05$).

Introduction

Adiponectin belongs to the family of adipokines, the proteins produced by the white adipose tissue. This tissue compartment is presently considered an active secretion organ and its derivatives have been shown to influence different physiological and pathological

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processes, including inflammation and degenerative conditions. Adiponectin together with leptin and resistin constitute the most actively surveyed particles of the adipokines group [1]. Adiponectin exerts a protective effect on blood vessels and is claimed to play a preventive role in obesity and atherosclerosis. Investigations have revealed its elevated concentrations in body fluids in rheumatic diseases and its effects on cells participating in inflammatory reactions [2, 3]. Adiponectin's function in inflammation and rheumatic disorders has not been clarified to date, but the protein is considered an important inflammatory modulator. As the pathogenesis of joint diseases is still not fully understood and these illnesses are not sufficiently controlled by contemporary medications, the question of adiponectin as a possible pathogenetic and/or therapeutic factor has lately emerged. It is of interest whether adiponectin concentrations differ between RA and other clinical conditions and if they are correlated with the intensity of inflammation and with results of laboratory findings as well as of physical examination. The present study was designed to contribute to the research.

Material and methods

Patients

A total of 44 consecutive female outpatients aged 38-81 years (average age 61 ±10) with definite or classic RA American Rheumatism Association (ARA) criteria [4] attending the Rheumatology Outpatient Department of the Central Clinical Hospital in Warsaw were included in the study. According to Larsen-Dale criteria [5] 6 patients were in stage 2, 27 in stage 3 and 11 in stage 4 of the disease. All of the patients were shown in radiological studies to have geodes and erosions on the joint surfaces and on bones close to the joints. The Disease Activity Index (DAS 28) was calculated from the formula in RA [6]. Two patients had a disease activity score (DAS) value between 2.4 and 3.7, and 42 patients had a DAS value over 3.7. The number of painful joints ranged from 3 to 14 (average: 8.3 ±2.8), and the number of swollen joints ranged from 1 to 11 (average: 4.9 ±2.4). Morning stiffness duration lasted on average 1.2 ±0.8 and ranged from 0.5 to 5 h. The disease duration ranged from 1 to 54 years (mean: 13.5 ±11.8 years).

A Waaler-Rose titre below 8 was confirmed in 2 (5%) patients (seronegative patients) and over 8 was confirmed in 42 (95%) (seropositives). Virtually all of the RA patients were taking non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatoid arthritis drugs (DMARDs): 21 taking leflunomide, 14 methotrexate, 5 sulphasalazine and 4 antimalarials. Thirty-nine (86.7%) patients were treated with low-dose prednisolone (< 10 mg daily).

The control group consisted of 42 patients aged 29-79 years (average age: 57 ±14 years); there were 42 women who attended the clinic at the same time with knee osteoarthritis according to the ARA [7] criteria. The duration of disease ranged from 1 to 18 years (mean 4.1 ±3.2 years). Twenty patients had bilateral knee osteoarthritis and 22 unilateral. The average Western Ontario and McMaster Universities (WOMAC) index pain scale score for the lower limbs [8] was 9.2 ±2.4. According to Kellgren and Lawrence's score [9], 18 patients were in stages 1 and 2, and 12 were in stages 3 and 4.

The blood was collected from 44 RA and 42 OA patients. Blood samples were collected into tubes without additives. The blood was allowed to clot for 2 h at room temperature and was then centrifuged and stored at –80°C. The study was approved by the local Research Ethics Committee.

Adiponectin measurements

Serum adiponectin level was determined using the Adiponectin Total ELISA kid – a solid phase enzyme-linked immunosorbent assay based on the sandwich principle [10]. The microtitre wells were coated with a monoclonal antibody directed toward a unique antigenic site on an adiponectin molecule. An aliquot of patient sample containing endogenous adiponectin was incubated in the coated well with a specific rabbit anti-adiponectin antibody. As a result, a sandwich complex was formed. After incubation, the unbound material was washed off and a rabbit peroxidase conjugate was added to detect the bound adiponectin. Having added the substrate solution, the intensity of colour, proportional to the concentration of adiponectin in the patient's sample, was assessed.

Other analyses

The following data were collected for all of the patients: the morphological composition of peripheral blood, the level of proteins and electrophoretic fractions in serum, ESR, phosphatase alkaline, electrolytes (Ca, P) and the serum adiponectin level. In RA patients, serological examinations were performed to discover the presence of rheumatoid factor in immunoglobulins (IgM), using Waaler-Rose's test, with over 8 as a positive level. Overall pain was assessed on a 100 mm visual analogue scale (VAS). The modified 28-joint disease activity score (DAS 28), including count of tenderness and swelling in 28 joints, and patient's self-report of global status on VAS were used.

Table I. Disease characteristics of RA and OA patients
Tabela I. *Charakterystyka pacjentów chorych na RZS i ChZS*

Parameters	RA group	OA group	p
disease duration [years]	13.5 ±11.8	4.1 ±3.2	< 0.0001
BMD – T-score	–1.79 ±0.90	–1.54 ±1.45	NS
ESR [mm/h]	35 ±21	12 ±8	< 0.0001
CRP [mg/l]	28.3 ±27.0	–	NA
α1-globulin [g%]	6.6 ±1.8	–	NA
α2-globulin [g%]	12.4 ±2.1	–	NA
β-globulin [g%]	13.4 ±1.8	–	NA
γ-globulin [g%]	16.0 ±4.3	–	NA
haemoglobin [g/l]	13.1±1.4	13.2 ±1	NS
erythrocytes [T/l]	4.4 ±0.4	4.4 ±0.3	NS
leukocytes [G/l]	8.5 ±2.8	6.1 ±1.6	< 0.0001
thrombocytes [G/l]	309 ±60	240 ±57	< 0.001
protein [g%]	7.0 ±0.5	7.0 ±0.3	NS
glucose [mg/dl]	82.7 ±15.7	85.0 ±10.3	NS
bilirubin [mg/dl]	0.55 ±0.21	0.49 ±0.19	NS
AspAT [U/l]	19.7 ±6.6	21.2 ±4.7	NS
AlAT [U/l]	19.6 ±7.6	21.4 ±8.1	NS
urea [mg/dl]	31.7 ±12	30.8 ±8.6	NS
creatinine [mg/dl]	0.75 ±0.21	0.72 ±0.12	NS
GFR [ml/min]	98.8 ±47.5	85.6 ±26.1	NS
uric acid [mg/dl]	4.2 ±1.4	4.5 ±0.8	NS
alkaline phosphatase [U/l]	87.9 ±46.1	71.5 ±28.4	NS
Ca [mmol/l]	2.35 ±0.34	2.32 ±0.14	NS
P [mg/dl]	3.30 ±0.62	3.11 ±0.45	NS
albumin [g/l]	50.9 ±5.8	–	NA
cholesterol [mg/dl]	216 ±55	206 ±37	NS
HDL [mg/dl]	62 ±16	57 ±21	NS
LDL [mg/dl]	124 ±49	121 ±32	NS
triglycerides [mg/dl]	127 ±55	111 ±38	NS

Radiographic method

All OA patients were examined by standing posteroanterior radiographs of both knee joints in semiflexion with fluoroscopic guidance and with almost all the load on the examined leg.

Densitometry examinations

Efficacy measurement included the femur ("total hip" and trochanter). BMD of the total hip T-score less than –2.5 was considered osteoporosis. Dual energy X-ray absorptiometry (DEXA) was the method for measuring BMD using a Lunar Prodigy (GE Medical Systems, Madison, WI, USA).

Statistical calculations

Statistical analyses were carried out using the statistical software package SPSS/PC+. The following tests were applied [11]:

1. The comparison of the clinical and laboratory variables was performed using ANOVA variance analysis and Student's t-test, or the non-parametric Kruskal-Wallis test and Wilcoxon score, which were used to compare continuous variables whose distributions in the sample were not Gaussian.

2. Correlation analysis was performed using Pearson's correlation coefficient or Spearman's rank correlation coefficient.

All reported P-values are two-sided and a type 1 error level of 0.05 was used [11].

Results

No statistically significant differences in blood biochemistry were noted between RA and OA groups, except that in RA patients the leukocyte counts were significantly higher than in OA individuals (respectively: 8.5 ±2.8 G/l and 6.1 ±1.6 G/l, $p < 0.0001$), and so were the platelet counts (309 ±60 G/l vs. 240 ±57 G/l, $p < 0.001$) (Table I). There were also no statistically significant differences in adiponectin concentrations between RA and OA groups. The serum level of adiponectin in RA and OA patients ranged respectively from 2.6 to 50 µg/ml (median 14.91) and 4.6 to 39.64 µg/ml (median 10.07) (Fig. 1).

No statistically significant differences in adiponectin concentrations were observed between RA patients of different stages of joint damage according to Larsen and Dale's scale or between those of long versus short disease duration (Fig. 2). According to the correlation coefficient, serum adiponectin level is independent of age of RA patients ($r = –0.18$; p = NS), number of painful joints ($r = 0.05$; p = NS), swollen joints

(r = 0.04; p = NS), duration of morning stiffness (r = 0.24; p = NS) and disease duration (r = 0.02; p = NS).

Out of all correlations between demographic and laboratory data and adiponectin concentrations recorded, only three were noted: a significant negative correlation for total serum protein in the RA group, and for uric acid in OA, as well as a significant positive correlation for cholesterol in OA were noted (Table II).

In both groups also a significant negative correlation between adiponectin concentrations and the T-score was observed (Table II).

Discussion

Adiponectin (ACRP30, AdipoQ, GBP28) is a biologically active 244-amino acid protein of a molecular weight of 28 kDa, coded by an ACDC gene (APM1), the transcript of which quantitatively predominates in adipocytes [1, 12]. Adiponectin's monomer is built of a C-terminal globular domain similar to C1q complement component and an N-terminal structure resembling collagens type VIII and X. Human serum contains three main adiponectin oligomers: of low (LMW), medium (MMW) and high (HMW) molecular weight [13]. An adipoR1 receptor on cell membranes binds mainly the adiponectin trimer (LMW) while an adipoR2 is recognised by higher oligomerized forms [13]. Adiponectin increases glucose cellular intake by an insulin-independent pathway, reduces muscle and liver lipid concentration and inhibits hepatic gluconeogenesis [14]. It enhances free fatty acids transport and oxidation, diminishes insulin resistance and increases high density lipoprotein (HDL) concentration. It also prevents atherosclerosis through inhibition of adhesion molecules, nitric oxide production and macrophage transformation into foam cells [15]. Adiponectin halts smooth muscle proliferation and migration and stimulates angiogenesis [15]. These findings highlight its beneficial role in vascular disorders and diabetes. Adiponectin also exerts a suppressive effect on liver fibrosis and tumour growth [16, 17]. The question of adiponectin's role in joint diseases is more complex, however. RA (and probably other inflammatory arthritides) develops as a result of disturbed balance between pro- and anti-inflammatory cytokines and other biologically active subcellular and cellular factors. Synovial macrophages and fibroblasts, Th1 lymphocytes, TNF-α, IL-1, IL-6, complement, C-reactive protein (CRP), matrix metalloproteinases (MMP) and leptin are known for their pro-inflammatory potential. Numerous investigations indicate that adiponectin can contribute

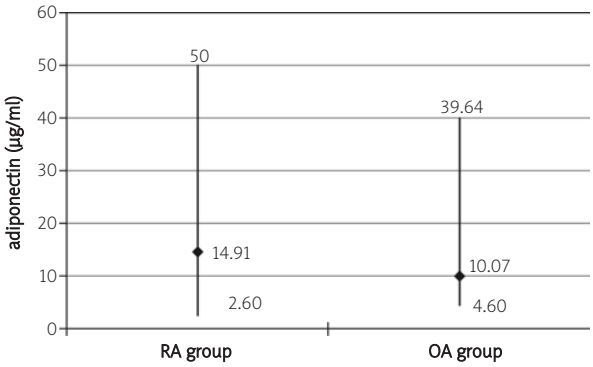

Fig. 1. Minimal, maximal and median adiponectin concentration in RA and OA groups.
Ryc. 1. *Minimalne, maksymalne i średnie stężenia adiponektyny w grupie chorych na RZS i ChZS.*

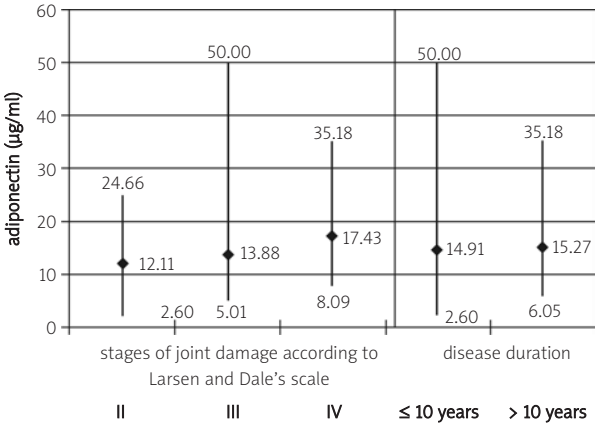

Fig. 2. Minimal, maximal and median adiponectin concentrations in different RA stages of joint damage according to Larsen and Dale's scale and different disease duration.
Ryc. 2. *Minimalne, maksymalne i średnie stężenia adiponektyny w różnych okresach RZS wg skali Larsena i Dala i w różnych czasach trwania choroby.*

to the inflammatory damage, too. Higher concentrations of this protein have been noted in sera, synovial fluid and synovial membranes of RA than in control patient groups [2, 18]. Immunohistochemistry revealed the expression of adiponectin, adipoR1 and adipoR2 in numerous synovial cells in RA. Synovial fibroblasts were shown to be rich in this protein [19]. Recombinant adiponectin was proved to stimulate IL-6 and monocyte chemotactic protein (MCP-1) synthesis

as well as oncogene-α expression in fibroblasts [19]. A similar pro-inflammatory effect was observed in chondrocytes [19]. HMW adiponectin structurally resembles TNF-α and complement proteins and therefore was suggested to contribute to inflammation genesis and protraction. Nevertheless, anti-TNF-α effects of adiponectin and a negative correlation between adiponectin and CRP were also noted [20].

Table II. Correlation between serum adiponectin level and examined laboratory data in RA and OA patients
Tabela II. *Korelacja między stężeniem adiponektyny w surowicy a badanymi parametrami u chorych na RZS i ChZS*

Parameters	RA Group		OA group	
	Pearson	Spearman	Pearson	Spearman
disease duration	0.02	0.29	0.33 (< 0.05)	0.43 (< 0.05)
BMD – T-score	–0.37 (p < 0.05)	–0.35 (p < 0.05)	–0.38 (< 0.05)	–0.42 (< 0.05)
ESR [mm/h]	–0.01	0.05	0.17	0.23
CRP [mg/l]	0.26	0.32 (p = 0.07)		
α1-globulin [g%]	0.17	0.29		
α2-globulin [g%]	0.25	0.18		
β-globulin [g%]	0.24	0.16		
γ-globulin [g%]	–0.25	–0.24		
haemoglobin [g/l]	–0.08	–0.09	–0.05	–0.22
erythrocytes [T/l]	–0.07	–0.05	–0.12	–0.16
leukocytes [G/l]	–0.04	–0.05	0.09	0.11
thrombocytes [G/l]	0.09	0.22	–0.04	–0.12
protein [g%]	–0.51 (< 0.01)	–0.38 (< 0.05)	0.26	0.06
glucose [mg/dl]	0.01	0.12	–0.36	–0.31
bilirubin [mg/dl]	–0.19	–0.16	0.20	–0.15
AspAT [U/l]	0.02	0.02	0.28	0.03
AlAT [U/l]	–0.15	–0.08	–0.31	–0.30
urea [mg/dl]	–0.29	–0.27	0.19	0.20
creatinine [mg/dl]	–0.21	–0.09	0.01	0.04
GFR [ml/min]	0.18	0.27	0.36	0.44
uric acid [mg/dl]	–0.14	–0.14	–0.48 (< 0.05)	–0.64 (< 0.005)
Ca [mmol/l]	–0.18	0.11	0.30	0.20
P [mg/dl]	0.03	0.11	0.01	0.10
alkaline phosphatase [U/l]	0.41 (< 0.05)	0.16	0.08	0.31
cholesterol [mg/dl]	–0.26	–0.32	0.38 (< 0.05)	0.43 (< 0.05)
HDL [mg/dl]	0.15	0.23	0.43 (< 0.05)	0.41 (< 0.05)
LDL [mg/dl]	–0.21	–0.19	–0.05	0.10
triglycerides [mg/dl]	–0.15	–0.12	–0.29	–0.34

Furthermore, adiponectin was proved to inhibit macrophage phagocytosis and myelomonocyte proliferation, as well as to promote metalloproteinase inhibitor transcription in fibroblasts [20]. Adiponectin mitigated the severity of collagen-induced arthritis in mice. TNF-α, IL-1β and MMP-3 expression decreased and IL-6 expression increased in synovial fibroblasts, but adiponectin significantly reduced IL-1β-stimulated fibroblast proliferation, despite increased IL-6 expression [21]. Adiponectin is suspected to counteract leptin in the development of inflammation [22]. Hypoadiponectinaemia was suggested to promote apoptosis and phagocytosis, thus acting as a triggering factor in the inflammatory processes [23]. It is also suspected that anti-TNF-treatment's beneficial effects can be partly linked to the drug-induced increase in adiponectin levels [20]. As both pro- and anti-inflammatory effects of adiponectin have been revealed to date, its role in rheumatoid arthritis and related conditions is still not fully understood. Reproducible results of investigations in this field however bring us nearer to these problems' solutions.

Our research showed no differences in serum adiponectin concentrations between RA and OA individuals. The finding seems confusing at first sight, yet it is consistent with that of Senolt *et al*. [3], who observed higher concentrations of adiponectin in RA compared to healthy controls, but similar ones between RA and OA individuals. Serum adiponectin concentrations in his research were not related to age, body mass index, disease duration, or disease activity in RA. We did not find any correlation between these variables either. Instead we observed a significant negative correlation between serum adiponectin and uric acid concentrations in the OA group. This is similar to recent results of Bo *et al*. [24] and Tamba *et al*. [25], whose survey, however, considered male populations. Our results showing a negative correlation between adiponectin and uric acid concentrations are also coherent with those of Oshima et al. [26]. We also showed a positive correlation between adiponectin concentrations and disease duration in OA, which may be related to adiponectin's protective role in osteoarthritis, proposed by Chen *et al*. in 2006 [27]. We also observed a significant negative correlation between serum adiponectin levels and bone mineral density (BMD). This is in accordance with other findings, where increasing levels of adiponectin were associated with a decrease in bone mass in women [28] and in men [29] and increased levels of resorption bone markers: alkaline phosphatase (ALP), bone cross-linked N-telopeptides of type I collagen (NTx) and carboxy-terminal telopeptide of type I collagen (CTx) [30]. One must keep in mind however that Oshima *et al*. in 2005 reported an adiponectin-driven increase in bone mineral density [26]. Taking all present and previous observations together, we conclude that adiponectin studies at such a "macroscopic" level are of only supportive value. Further investigations on molecular and receptor levels are necessary to elucidate the influence of this adipokine on bone and joint diseases.

Conclusion

No strict correspondence between serum adiponectin concentrations and the type of joint disease or patient characteristics can be inferred from the study, except adiponectin's correlation with bone loss in both investigated groups.

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