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Adipokines in rheumatoid arthritis patients suffering glomerulonephritis

Abstract

Background: Beside their eminent role in metabolic syndrome, white adipose tissue (WAT) derived adipokines might have a distinguished role in autoimmune and rheumatic diseases. In addition, increased level of many adipokines is observed in patients suffering glomerulonephritis. The status of adipokines was not studied in rheumatoid arthritis patients (RA) suffering glomerulonephritis (GN).

Objective: To study serum level of adiponectin, leptin, and Visfatin in RA patients suffering GN in a trial to elucidate if they play a role on metabolic or endothelial function.

Cases and methods: In this cross-sectional case control observational study, we compared serum level of adiponectin, leptin, and Visfatin in fifty RA patients (group I) in coparison to fifty RA cases suffering chronic GN (group II) and fifty normal control subjects. In addition, we looked for kidney function tests and 24 urine protein (UP), serum calcium, phosphorus, alkaline phosphatase (AP), 25 hydroxy vitamin D (25 OH vit. D), parathyroid hormone (PTH), C-reactive protein (CRP), interleukin 6(IL6), lipid profile, and Homa insulin resistanc (Homa IR). RA cases were further investigated for rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) carotid arteries intima media thickness (IMT), brachial artery flow mediated Dilation (BA-FMD), health assessment questionnaire (HAQ), disease activity score calculator (DASC), simple disease activity index (SDAI), and clinical disease activity index (CDAI). Percutaneous kidney biopsies were obtained in group II patients.

Results: Serum adiponectin and Visfatin are significantly higher and serum leptin is significantly lower in Group II compared to group I and the control group (20.3 vs. 18.6 and 12.3, 24,5 vs. 20.9 and 9.8, and 3.6 vs. 4.6 and 7.8 ng/mL for median serum adiponectin, visfatin, and leptin in group II vs group I and control group respectively, P<0.001 in all). Serum level of 25 (OH) vit D is significantly lower, while serum AP, PTH and Homa IR are significantly higher in group I compared to control subjects (18 vs. 37 ng/mL, 140.5 vs, 57 u/L, 63 vs 47.8 ng/mL, and 13.2 vs 4 respectively, P<0.001 in all) whilst there is no significant difference in these parameters between the RA groups. BA-FMD is significantly lower in group II vs group I (3% vs 4%, P=0.02) but there are no significant differences between these two groups in IMT of carotid arteries, HAQ, DASC, SDAI or CDAI. Moreover, there is no difference in any of the studied parameters within patients of group II according to renal histopathology.

Conclusion: Studied adipokines have no relation to metabolic or vascular complications of RA. Changes of serum adipokines in GN patients are unrelated to inflammation. This pilot study would stimulate further research looking for the possible role of different adipokines in GN complicating RA.

Keywords: rheumatoid arthritis, glomerulonephritis, adipokines, adiponectin, leptin, visfatin, homa-IR, FMD, IMT

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Abbreviations: WAT, white adipose tissue; RA, rheumatoid arthritis patients; GN, suffering glomerulonephritis; AP, alkaline phosphatase; UP, urine protein; PTH, parathyroid hormone; CRP, C-reactive protein; IL6, interleukin 6; Homa IR, homa insulin resistanc; 25 OH vit.D, 25 hydroxy vitamin D; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide; IMT, intima media thickness; BA-FMD, brachial artery flow mediated Dilation; HAQ, health assessment questionnaire; DASC, disease activity score calculator; SDAI, simple disease activity index; CDAI, clinical disease activity index; NSAIDs, nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs; MCNS, minimal change nephrotic syndrome; MN, membranous nephropathy; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative GN; SLE, systemic lupus erythematosus; HPLC, high-performance liquid chromatography; SPSS, Statistical Package for Social Science; IQR, interquartile range; BMI, Body mass index

Introduction

RA is a systemic autoimmune inflammatory disease primarily involving the joints and is more prevalent in females.[1] Renal manifestations encountered in RA are mainly attributed to the nephrotoxicity of anti-rheumatic medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs).[2] Glomerulonephritis, interstitial nephritis, vasculitis and tubular necrosis can be encountered in RA patients. The most famous glomerular diseases encountered among RA include minimal change nephrotic syndrome (MCNS), mesangioproliferative GN (IgA and non IgA), membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS), membranoproliferative GN (MPGN), crescentic GN, and renal amyloidosis.[3] Long standing elevation of IL6 has been implicated as a possible link between RA and mesangiioproliferative GN.[4]

Since the discovery of leptin in 1994, WAT is not considered anymore as inert fat depot. Its role as a contributor in whole body homeostasis has consistently grown.[5] WAT is the main source of many biologically active hormones that are collectively called adipokines.[6] Although adipokines are generally found within the adipocytes of WAT, they can be synthesized at other sites and can participate in many functions unrelated to WAT.[7] Furthermore, macrophages are components of adipose tissue. They do participate in activities related to WAT as cross-talk between adipocytes and lymphocytes and can thus lead to immune regulation. In addition to leptin, adiponectin, resistin, and visfatin, adipose tissue produces and releases a variety of cytokines and chemokines, such as tumor necrosis factor (TNF)-alpha, IL-6, monocyte chemoattractant protein 1 (MCP1), and others.[8] Increased serum levels of adiponectin, leptin, and visfatin have been observed in RA.[9] Serum leptin was positively associated with CRP level in RA patients, suggesting that adipokines may have a pro-inflammatory role in this disease.[10] Other *in vitro* studies have demonstrated that adiponectin stimulates rheumatoid synovial fibroblasts to secrete interleukin 8 and prostaglandin E.[11,12] In addition, previous studies suggested a significant positive correlation between serum leptin and RA activity.[13] On the other hand, interleukin-1 β (IL-1β) and tumour necrosis factor – α (TNFα) stimulate the secretion of leptin by the preadipocytes.[14] However, IL-1β induces long-lasting inhibition of leptin release by adipocytes and leptin gene expression within these cells.[15]

When serum leptin and adiponectin were tested in systemic lupus erythematosus (SLE) patients with and without nephritis, significantly higher serum level of adiponectin was detected in patients suffering lupus nephritis.[16] The severity of proteinuria correlated with serum adiponectin in the lupus nephritis group.[17] Similar studies in RA patients are lacking.

Aim of work

The aim of this study is to elucidate the serum level of adiponectin, leptin, and visfatin in RA patients, looking for the impact of chronic GN affecting these patients on the serum level of these adipokines. We will also for the possible effect of these adipokines on insulin resistance and endothelial function in RA patients.

Patients and methods

This is a cross sectional case control observational study that was run on 100 RA cases and 50 normal control subjects. Fifty cases of RA patients also suffering chronic GN (group II) were compared to 50 RA patients with normal kidney functions (group I). Kidney biopsy was done to group II patients. The biopsy results were used to look for any discrepancy in the studied parameters according to histopathology pattern among group II patients. All 150 subjects underwent thorough history taking and clinical examination after signing an informed consent. This was followed by analysis for serum adiponectin, leptin, visfatin, urea, creatinine, urea, uric acid, calcium, phosphorus, alkaline phosphatase, PTH, 25 (OH) vit D, CRP, IL6, cholesterol, triglycerides, HDL cholesterol, LDL cholesterol as well as complete blood count and estimation of Homa IR. RA patients were inquired as regards disease duration, medication history and additionally studied for RF, anti-CCP, internal carotid IMT, BA-FMD, HAQ, DASC, SDAI, and CDAI. HAQ and 28 tender and swollen joint counts were recorded for all patients. HAQ was calculated and scored as mild (HAQ < 1.3), moderate (1.3 < HAQ < 1.8), and severe (HAQ > 1.8) functional losses.[18] DASC was graded as follows: DASC ≤ 2.6 = clinical remission, ≤ 3.2 = low disease activity, ≤ 5.1 = moderate disease activity, and > 5.1 = high disease activity.[19] SDAI was graded ad follows: SDAI ≤ 3.3 = clinical remission, >3.3 to ≤ 11 = low disease activity, >11 to ≤ 26 = moderate activity, > 26 = high disease activity. CDAI was graded ad follows: CDAI ≤ 2.8 = clinical remission, >2.8 to ≤ 10 = low disease activity, >10 to ≤ 22 = moderate activity, > 22 = high disease activity.[20]

The serum 25 (OH) vit D was measured using high-performance liquid chromatography (HPLC). The serum level of iPTH was evaluated using enzyme amplified sensitivity immunoassay (Roche Diagnostics, Indianapolis, IN). RF and anti-CCP were considered positive when their concentrations were higher than the cut-off value of the kit (15 IU/ml for RF and 20 U/ml for anti-CCP); high titer was considered if the level is 3 times upper the cut-off value. Internal carotid IMT and BA-FMD were performed using B-mode SIEMENS ACUSON X300 ultrasonography. The diameter of the brachial artery (BA) was measured at rest initially (Di). Then, obliteration of the brachial artery was accomplished by inflating the pneumatic cuff 50 mmHg above systolic blood pressure for one minute. The cuff was then deflated and BA diameter was re-measured after 60 seconds post deflation (DF). FMD was then calculated using the equation FMD = [(Df –Di)\ DI] x 100.

Statistical analysis

The data collected were analyzed using IBM Statistical Package for Social Science (SPSS) Statistics 22. When data were tested for normality, most for the data are not normally distributed. Values are expressed, accordingly, as mean, median, and interquartile range (IQR). Mann-Whitney test was used to compare groups. Spearman univariate analysis was used to find out the possible significant associations of serum adiponectin, leptin, and visfatin with the other studied parameters. For qualitative data, bivariate associations were examined using chi-square test.

Results

Results are summarized in Table 1–4 and Figure 1. There is no significant difference in age between the different groups. There is no difference between groups I and II in gender, special habits, encountered comorbidities, rheumatoid factor or anti-CCP. The spectrum of anti-rheumatic agents used in RA patients included prednisolone, NSAIDs, methotrexate, leflunamide, hydroquin, sulfasalazine, and cyclosporine. Apart from the significantly increased number of patients in group I that were consuming leflunamide, there is no significant difference between the two groups in the consumption of any of the other anti-rheumatic agents Table 2. Details of renal histopathology of group II patiens is demonstrated in Figure 1B.

Apart from serum calcium, phosphorus, and uric acid there is a significant difference in all other studied parameters between group I patients and normal control group Table 1. There is no significant difference between group I and group 2 in HAQ, DASC, SDAI, CDAI, duration of RA, serum uric acid, calcium, alkaline phosphatase, Alanine transaminase, aspartate transaminase, total cholesterol, LDL cholesterol, ESR, CRP, IL6, 25 (OH) vit D, PTH, Homa IR, complete blood count, carotid arteries intima media thickness, dose of steroid, hydroquin, or methotrexate. Body mass index (BMI), serum urea, creatinine, phosphorus, UP, serum triglycerides, serum adiponectin, and serum visfatin are significantly lower, while dose of luflonamide, HDL cholesterol, serum leptin, and BA-FMD are significantly higher in group I than group II Table 3, Significant positive correlation was encountered between either serum adiponectin or serum visfatin on one hand and BMI on the other. A significant positive correlation is also encountered between serum visfatin and serum creatinine, serum phosphorus, and rheumatoid factor titer. Serum leptin showed

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significant negative correlations with BMI, serum creatinine, and serum phosphorus Table 4. We did not find any significant difference in any of the studied parameters among different subdivisions of group II based on renal histopathology.

Table 1 comparative analysis of group I versus normal control subjects

Item	Group I (50)		Control (50)		Z score	P
	Range	Mean, median, IQR	Range	Mean, median, IQR		
Age (years)	25-70	46.5,47,14.5	28-73	45.9,42,13.5	0.86	0.38
BMI (kg/m^2)	18-30	23.5, 23, 1.85	17.5-28	29.9, 24, 4	-1.7	0.097
S. urea (mg/dL)	Oct-45	22.6, 22, 9	17-Oct	13.3, 13, 4	5.57	<0.001
S.creatinine(mg/dL)	0.28-1.6	0.7,0.7.0.3	0.6-0.9	0.8,0.75,0.1	-2.1	0.037
S.UA (mg/dL)	3.7-7.9	5.1, 4.8, 1.6	4 -5.5	4.7, 5.5, 1.1	1.4	0.16
S.calcium (mg/dL)	7,4-10.7	8.9, 8.9, 0.8	8.5-9.5	9, 8.9, 0.7	-1.23	0.22
S. phosph. (mg/dL)	2.4-4.9	3.6, 3.7, 1	3.4 - 4	3.7, 3.6, 0.5	0.24	0.8
S.Alk.Ph. (u/L)	115- 165	139, 140.5,10	39 - 86	60.9, 57, 24.3	8.6	<0.001
Hemoglobin (g/dL)	8.4 – 15.6	11.7,11.8,1.6	11.8-14.5	12.8,12.8,1.2	-4.2	<0.001
WBC count (x10^3/mm^3)	2 – 13,9	7.2, 6.5, 3.9	7-Apr	5.7, 6.2, 1.7	2.1	<0.04
Plt. count (x103/mm^3)	151-594	304, 294, 108	236 -422	349, 325, 94	-3.6	<0.001
ESR (mm/hour)	8 - 120	58, 52, 41	11-Feb	3.9, 4, 2	8.6	<0.001
CRP (mg/dL)	0 – 71.9	5.9, 2, 3.9	0.2 - 2	0.8, 0.7, 0.8	5.2	<0.001
IL6 (pg/mL)	21 - 41	22, 25, 6.7	5.3 – 9.6	7, 6.55, 1.9	8.6	<0.001
25 (OH) vit D (ng/mL)	8.7 - 32	17.9, 18, 9	31.8 – 42.8	36.6, 37, 5.8	-8.58	<0.001
S.PTH (ng/mL)	44.3 – 99.4	65.6, 63, 21.7	44 – 51.4	47.9, 47.8, 4.35	7.88	<0.001
Homa IR	7.4 - 25	13.6, 13.2, 6.3	3.3 – 4.5	4, 4, 0.45	8.6	<0.001
S.Adiponectin (ng/mL)	16 - 20	18.4, 18.6, 1.9	11.3-12.7	12.2, 12.3, 0.5	8.6	<0.001
S. Leptin (ng/mL)	3.5-5.5	4.5, 4.6, 1.1	6.8 – 8.6	7.8, 7.8, 0.8	-8.6	<0.001
S.Visfatin (ng/mL)	18 - 22	20.6, 20.9, 1.3	6.7 – 12.4	10, 9.8, 2.5	8.6	<0.001

BMI, body mass index; S.UA, serum uric acid; S. phosph., serum phosphorus; S.ALK ph., serum alkaline phosphatase; WBC, white blood cell; Plt, platelet; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL6, interleukin 6; 25(OH) vit D, 25 hydroxy vitamin D; S.PTH, serum parathyroid hormone; Homa IR, Homa insulin resistance.

Table 2 Comparative analysis of demographic, therapeutic and laboratory data in rheumatoid patients using chi square test

Variable		Group I (50)		Group II (50)		P
		Numer	Percent	Numer	Percent	
Gender (Female/Male)		44/6	88/12	40/10	80/20	0.28
Smoking		1	2	2	4	0.57
Major co-morbidities						
Diabetes mellitus		2	4	3	6	0.648
Hypertension		7	14	8	16	0.78
Interstitial lung disease		7	14	4	8	0.34
Anti-rheumatic agents						
prednisolone		32	64	32	64	1
NSAIDs		3	6	8	16	0.11
Leflunomide		31	62	17	34	0.0053*
Hydroxychloroquine		19	38	18	36	0.84
Methotrexate		33	66	29	58	0.41
Sulfasalazine		3	6	3	6	1
Cyclosporine		1	2	0	0	0.32
Rheumatoid factor	**Negative**	21	42	12	24	0.057
	≤3Upper Limit of Normal	18	36	22	44	0.42
	>3 Upper Limit of Normal	11	22	16	32	0.26
Anti-citrullinated protein antibodies	**Negative**	23	46	25	50	0.69
	≤3Upper Limit of Normal	17	34	16	32	0.83
	>3 Upper Limit of Normal	10	20	9	18	0.8

NSAIDs, non-steroidal anti-inflamatory agents

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Table 3 Comparative analysis of demographic, therapeutic and laboratory data in rheumatoid patients using Mann-Whitney U Test

Item	Group I (50)		Group II (50)		Z score	P
	Range	Mean, median, IQR	Range	Mean, median, IQR		
Age (years)	25-70	46.5,47,14.5	18 - 74	43.8, 42, 16.8	1.2	0.22
BMI (kg/m^2)	18-30	23.5, 23, 1.85	23 - 29	25.6, 25, 4	-5.16	<0.001
Duration of RA (years)	0.25 - 34	8.6, 5.5, 12	0.83 -30	7.3, 5.5, 8.3	1.12	0.26
Prednisolone (mg/day)	0 - 15	4.9, 5, 10	0 - 20	5.5, 5, 10	-0.22	0.83
Leflunomide (mg/day)	0 - 20	12.4, 20, 20	0 - 20	6.8, 0, 20	2.5	0.012
Hydroquin (mg/day)	0 - 400	136, 0, 400	0 - 400	105, 0, 200	0.52	0.54
MTX (mg/week)	0 - 25	9.2, 11.3, 12.5	0 - 25	10, 12.5, 18.1	-0.37	0.71
S. urea (mg/dL)	Oct-45	22.6, 22, 9	10 - 182	43.5, 30, 30.5	-3.6	<0.001
S.creatinine(mg/dL)	0.28-1.6	0.7,0.7.0.3	0.4 – 5.3	1.2, 0.95, 0.8	-4.2	<0.001
S.UA (mg/dL)	3.7-7.9	5.1, 4.8, 1.6	2.5 – 8.2	4.97, 5, 2	0.08	0.94
S.calcium (mg/dL)	7,4-10.7	8.9, 8.9, 0.8	7.8 – 10.3	9 , 9, 0.8	-0.94	0.35
S. phosph. (mg/dL)	2.4-4.9	3.6, 3.7, 1	2.4 - 5	4, 4, 0.5	-3.5	<0.001
S.Alk.Ph. (u/L)	115- 165	139, 140.5,10	126 - 152	138, 139, 9.5	0.7	0.47
Hemoglobin (g/dL)	8.4 – 15.6	11.7,11.8,1.6	7.1 – 13.5	11.2, 11.5, 2.2	1.6	0.12
WBC count (x10^3/mm^3)	2 – 13,9	7.2, 6.5, 3.9	2.4 – 18.9	7.1, 6.3, 4	0.39	0.7
Plt. count (x10^3/mm^3)	151-594	304, 294, 108	151 - 541	312, 290, 202	0.15	0.87
S.ALT (U/L)	7 - 170	28.6, 18, 12.3	Jun-84	22.4, 20, 13.5	-0.05	0.96
S.AST (U/L)	7 - 121	29.5, 24.5, 10.8	May-78	23.8, 21.5, 12.5	1.37	0.17
24 U. Ptn (g/day)	0.1 – 0.4	0.23, 0.2, 0.2	1.7 - 5	2.6, 2.5, 1	-8.6	<0.001
S. Cholesterol (mg/dL)	100 -291	187, 181, 52	105 - 280	185, 189, 24	-0.65	0.52
S. HDL-c (mg/dL)	Oct-81	48, 49, 20	26 - 76	44, 41, 10	2.03	0.04
S. LDL-c (mg/dL)	57 - 200	118, 113, 53	60 - 193	112, 108, 34	0.9	0.36
S.TG (mg/dL)	45 - 472	126,116, 51	34 - 328	145, 150, 49	-2.84	0.004
ESR (mm/hour)	8 - 120	58, 52, 41	10 - 135	51, 42.5, 49	1.2	0.27
CRP (mg/dL)	0 – 71.9	5.9, 2, 3.9	0.1 – 19.3	3.3, 1.4, 4.4	1.48	0.14
IL6 (pg/mL)	21 - 41	22, 25, 6.7	21 - 41	27.7, 25.2, 9.6	-0.47	0.64
25 (OH) vit D (ng/mL)	8.7 - 32	17.9, 18, 9	6.8 - 27	16.4, 17, 9	0.131	0.19
S.PTH (ng/mL)	44.3 – 99.4	65.6, 63, 21.7	45 – 99.4	68, 63, 29	-0.68	0.5
Homa IR	7.4 - 25	13.6, 13.2, 6.3	7.3 – 21.3	12, 10.6, 5.5	1.9	0.056
S.Adiponectin (ng/mL)	16 - 20	18.4, 18.6, 1.9	18 - 22	20.2, 20.3, 1.8	-6.1	<0.001
S. Leptin (ng/mL)	3.5-5.5	4.5, 4.6, 1.1	2.5 – 4.4	3.6, 3.6, 0.7	6.45	<0.001
S.Visfatin (ng/mL)	18 - 22	20.6, 20.9, 1.3	20.6 - 29	24.6, 24.5, 3.3	-7.7	<0.001
Rt. Carotid IMT (cm)	0.05 – 0.12	0.08, 0.08, 0.02	0.05 – 0.11	0.08, 0.08, 0.02	-0.79	0.43
Lt. carotid IMT (cm)	0.04 – 0.14	0.08, 0.08, 0.02	0.04 – 0.15	0.08, 0.08, 0.02	0.15	0.88
BA-FMD (%)	0 - 14	5.1, 4, 4	0 - 18	4.1, 3, 5.5	2.3	0.02
HAQ	0 - 3	0.8, 07, 1.3	0 - 3	1, 1, 1.1	-1	0.3
DAS 28	1.73 – 7.72	4.7, 4.7, 1.6	1.9 - 6.9	4.6, 4.5, 2.2	-0.003	1
SDAI	3.8 - 54	21, 17.5, 18.5	0.3 - 59	23.3, 23.5, 20.8	-0.9	0.37
CDAI	Feb-53	17.9, 16, 15.3	0 - 66	21.1, 18.5, 17.5	-96	0.34

BMI, body mass index; RA, rheumatoid arthritis; S.UA, serum uric acid; S. phosph., serum phosphorus; S.ALK ph., serum alkaline phosphatase; WBC, white blood cell; Plt., platelet; ALT, alanine transaminase; AST, aspartate transaminase; 24 U Ptn, 24 hours urine protein; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL6, interleukin 6; 25(OH) vit D, 25 hydroxy vitamin D; S.PTH, serum parathyroid hormone; Homa IR, Homa insulin resistance; Rt, right; IMT, intima-media thickness; Lt, left; BA-FMD, brachial artery flow mediated dilation; HAQ, health assessment questionnaire; DAS28, disease activity score 28; SDAI, simple disease activity index; CDAI, clinical disease activity index.

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Table 4 Correlations of plasma level of adiponectin, serum leptin and serum visfatin with different variables serum phosphorus among RA patients§, using spearman's rho test

Variables in all patients with RA (100)	Plasma Adiponectin		Serum Leptin		Serum Visfatin	
	r_s	P (2-tailed)	r_s	P (2-Tailed)	r_s	P (2-Tailed)
Age	-0.12	0.3	0.15	0.1	-0.1	0.2
BMI (Kg/m^2)	0.29	0.004*	-0.3	0.002*	0.4	1E-05*
Duration of RA (years)	-0.12	0.3	0.04	0.7	-0.15	0.1
Onset of renal disease from onset of RA (months)	0.06	0.5	-0.06	0 .5	0.06	0 .5
S. Creat. (mg/dL)	0.12	0.3	-0.24	0.01*	0.3	0.0003 *
S.UA (mg/dL)	0.08	0.4	0.16	0.1	-0.04	0.7
S.calcium (mg/dL)	0.13	0.2	0.18	0.06	0.1	0.2
S. phosph. (mg/dL)	0.22	0.035*	-0.23	0.02 *	0.3	0.005 *
S.Alk.Ph. (u/L)	-0.04	0.7	0.21	0.038*	0.03	0.8
24 U. Ptn (g/day)	0.2	0.2	0.02	0.9	0.02	0.9
ESR (mm/hour)	-0.09	0.3	0.05	0.6	-0.1	0.1
CRP (mg/dL)	0.06	0.5	0.1	0.3	-0.1	0.2
R.F. (IU/mL)	0.05	0.6	-0.02	0.8	0.2	0.02 *
Anti-CCP (U/mL)	-0.04	0.7	0.13	0.2	-0.01	0.9
25 (OH) vit D (ng/mL)	-0.18	0.08	0.007	0.9	-0.1	0.2
S.PTH (ng/mL)	0.12	0.2	-0.1	0.2	0.07	0.5
IL6 (pg/mL)	0.04	0.7	-0.05	0.6	-0.04	0.7
Homa IR	-0.15	0.1	0.1	0.09	-0.07	0.5
Carotid IMT (cm)	0.1	0.3	-0.006	0.9	0.03	0.8
BA-FMD (%)	-0.11	0.3	0.1	0.05	-0.15	0.1
HAQ	0.07	0.5	-0.07	0.5	-0.006	0.9
DAS28	-0.01	0.89932	-0.02	0.8	-0.1	0.3
SDAI	0.07	0.5	-0.04	0.7	-0.005	0.9
CDAI	0.07	0.5	-0.02	0.9	-0.02	0.9

§ With the exception of 24 U Ptn that was performed among group II only. BMI, body mass index; RA, rheumatoid arthritis; S.creat., serum creatinine; S.UA, serum uric acid; S. phosph., serum phosphorus; 24 U Ptn, 24 hours urine protein; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; Anti-CCP, Anti–cyclic citrullinated peptide; 25(OH) vit D, 25 hydroxy vitamin D; S.PTH, serum parathyroid hormone; IL6, interleukin 6; Homa IR, Homa insulin resistance; IMT, intima-media thickness; BA-FMD, brachial artery flow mediated dilation; HAQ, health assessment questionnaire; DAS28, disease activity score 28; SDAI, simple disease activity index; CDAI, clinical disease activity index

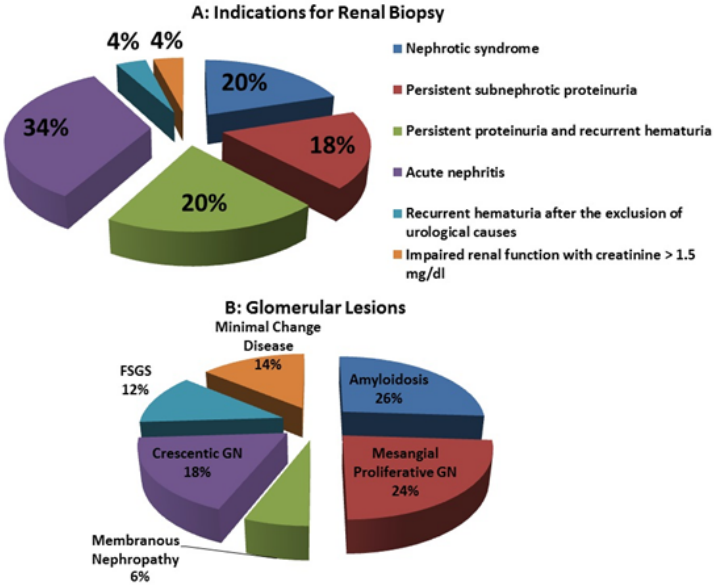

Figure 1 Renal biopsies for group II.

A: Indications for Renal Biopsy

B: Glomerular Lesions

GN, Glomerulonephritis; **FSGS**, focal segmental glomerulosclerosis

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Discussion

Many members of the adipokine family exhibit pro-inflammatory characteristics, including suppression of T-cells apoptosis and enhancement of T-helper 1 cell activation, leading to increased production of pro-inflammatory cytokines and monocytes activation.[21] We observed increased level of adiponectin, and visfatin in RA patients in comparison to the normal control group with further significant increase in the level of these three adipokines in RA patients suffering GN. On the contrary, serum leptin is significantly lower in patients of group II in comparison to group I and in group I compared to normal control group. This is the first study of serum adipokines in RA patients suffering GN. Increased level of serum adiponectin in RA cases suffering GN simulates the observation in SLE patients suffering Lupus nephritis.[16,17] Contrary to the significant correlation between serum adiponectin and intensity of proteinuria,[17] the current study failed to encounter any significant correlation between the magnitude of urine protein and any of the studied adipokines among group II patients. It is worth mentioning that there is discordance about the association of adiponectin and proteinuria in lupus nephritis patients. Rovin et al.,[16] failed to identify significant correlation between serum adiponectin and severity of proteinuria in the multivariate analysis.[16] In spite of the significant increase of serum adiponectin and visfatin and the significant decrease of serum leptin in patients of group II versus group I, there was no significant difference between the two groups in ESR, CRP, IL6, HAQ, DASC, SDAI, CDAI, or duration of RA. This observation should cast doubt about the role of these adipokines in pathogenesis of inflammation among RA patients. The absence of significant correlation between the individual adipokines on one hand and different studied inflammatory markers and indices of RA activity gives support to this impression. The significant changes of different adipokines observed in patients of group II is possibly more related to the significant difference in BMI between the two groups or as a consequence of renal disease. In patients not suffering RA, adipokines increase in chronic kidney disease patients,[22,23] and patients developing GN.[24,25] The current study shows a significant correlation of the 3 adipokines studied and BMI. A significant correlation is also encountered between serum creatinine, serum leptin and serum visfatin. The absence of a significant difference in Homa IR or IMT of carotid arteries between the 2 RA groups in spite of the sigmificant difference in serum adipokines might obviate the role of these cytokine in insulin resistance or vascular complications encountered in this disease. The absence of any significant correlation between Homa IR or IMT and the different adipokines favors this opinion. Meanwhile, the significant difference in endothelial function observed between the two RA groups seems unrelated to increased adipokines. Previous studies have disclosed the intimate relation between glomerulonephritis and endothelial dysfunction.[26,27]

The significant differences in serum urea and creatinine between group I and normal control subjects is likely related to steroid treatmen. The increased number of patients consuming leflunomide by patients devoid of GN might pinpoint to a possible role of this agent to prevent GN. Leflunomide decreases proteinuria and improves renal function in GN cases.[28] The consistent strong association between serum phosphorus and the different adipokines in absence of similar association of adipokines with serum calcium, alkaline phosphatase or PTH deserves future investigation to confirm or preclude this relation. On thorough search of the literature, a similar association between adipokines and serum phosphorus is not encountered.

Based on our findings, it seems that changes encountered in the serum level of adipokines has no impact on the metabolic or vascular consequences of RA, exaggerated changes in serum adipokines encounyered in RA patients suffering GN is more likely related to BMI or their renal disease. It seems the the systemic inflammatory state encountered in RA patients has minimal role, if any, on development of GN complicating this disease.

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None.

Conflicts of interest

The authors declares that there is no conflict of interest.

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