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Assessment of Serum Level of High-Molecular-Weight Adiponectin (HMW-APN) in Rheumatoid arthritis Patients and Its Correlation with the Disease Activity

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disorder, which is associated with joint deformity and functional impairment. Paradoxically, the pathogenesis of RA adiponectin appears to have proinflammatory activities in the joints, being able to induce the release of inflammatory mediators and may also be linked to disease activity.

Objective: To assess serum concentration of high-molecular-weight APN (HMW-APN) in RA cases and its association with disease activity.

Methods: This cross sectional case-control study included 80 persons that were divided into 2 groups; group A (patients' group) that involved 40 RA cases and group B that included 40 normal persons with matched age and sex. Serum level of high-molecular-weight adiponectin was assessed using ELISA technique. Plain X-ray on both hands to detect bone erosion was assessed by Larsen Score.

Results: Serum levels of HMW-APN were significantly higher in RA cases in comparison with controls. A significant positive correlation existed between HMW APN with number of swollen joints and Disease Activity Score-28 for Rheumatoid Arthritis with ESR (DAS28-ESR), ESR, Rheumatoid factor, anti-cyclic citrullinated peptides (CCP) antibodies and Larsen Grading Scale. According to the ROC analysis, the best cutoff point of serum HMW-APN to identify RA from healthy control was > 77.04 Pg/ml. This point showed high sensitivity (87.5%) with moderate specificity (70%) and AUC (0.883).

Conclusion: Serum levels of HMW-APN could be used as reliable biomarker in diagnosis of RA in addition to determination of the disease activity.

Keywords: HMW-APN, RA, DAS-28 with ESR, Rheumatoid factor.

INTRODUCTION

RA is a chronic autoimmune symmetrically polyarthritis disease, which is characterized by tenosynovitis, cartilage damage and bony erosions. Until the 1990s, RA has been associated with disabilities, inability to work, and high mortalities. However, newer treatments have made RA a treatable condition. A significant progress has been made in the development of disease-modifying anti-rheumatic drugs, which control the inflammatory process and thus prevent further joint destruction [1]. In general, the aim of RA treatment is to improve the quality of life through improving the pain, maintaining functional ability, and thus preventing disability [2].

Adiponectin is an anti-inflammatory adipokine formed of 244 amino acids and is released predominantly by adipocytes. Studies suggested that monomeric form of adiponectin seems to occur only in adipocytes, however there are 3 circulating forms of adiponectin in human plasma: trimmer (low molecular weight, LMW), hexamer (medium molecular weight, MMW) and multimer (high molecular weight, HMW) [3, 4].

Many studies highlighted the important role of adiponectin in obesity, diabetes, atherosclerosis and metabolic syndrome, being the highest levels a protective factor for such conditions [5]. Recently, the role of adipokines in the pathomechanism of RA has been investigated however results remain conflicting.

Though, many studies have proven the implications of adipokines in the pathophysiology of autoimmune disorders, such as RA, their role in the pathomechanism of disease progression is unclear [2]. Paradoxically, in RA, adiponectin appears to possess pro-inflammatory effects in the joints since it is able to induce the release of inflammatory mediators and might also be linked to disease activity [6]. Adipokines have been found to have a significant role in RA pathophysiology [7]. **Hutcheson**, points out that knowledge about adiposity has changed and currently it is considered as a significant regulator of many pathophysiologic processes, such as inflammation. Moreover, adipokines regulate the appetite and glucose metabolism [8].

This study aimed at assessing the serum level of HMW-adiponectin in RA patient and its relationship with disease activity.

SUBJECTS AND METHODS

This was a cross sectional case-control study. We collected the subjects from the Outpatient Clinic and Inpatient Department of Rheumatology and Rehabilitation, Mansoura University Hospitals. Our study was conducted for one year from November 2021 to November 2022. It included 80 subjects that were allocated into 2 groups; group A (patients' group) involved 40 cases with RA aged 18 years or more and fulfilled the 2010 American College of Rheumatology European League Against Rheumatism classification

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criteria for RA [9], but we did not enroll cases with diabetes, atherosclerosis, infections, malignancy, with other autoimmune diseases rather than RA and obese patients (BMI > 30) and Underweight patients (BMI < 18). Group B was the control group of 40 normal persons with matched age and gender to the patients group.

Methods

All cases were subjected to complete history taking and thorough physical examination included general and local examination of joints. Laboratory tests included CBC, ESR, C-RP, rheumatoid factor, anti-cyclic citrullinated peptide, liver function tests and kidney functions tests.

Determination of disease Activity

Rheumatoid disease activity was evaluated by DAS28-ESR. DAS28-ESR employing a simplified 28-joint count [10].

Radiological Assessment

Plain X-ray on both hands to detect bone erosion assed by **Larsen Score** [11]. Scoring was performed using the Larsen scoring system with a score (0–5) assigned to each of the proximal interphalangeal and metacarpophalangeal joints, the 1st interphalangeal joints, the 2nd to 5th metatarsophalangeal joints and to each wrist, with the wrist scores being multiplied by 5 when calculating the overall Larsen score. This gave an overall Larsen score ranging from 0 to 250.

Measurement of serum level of HMW-APN

HMW-APN level was measured using a commercial enzyme-linked immunosorbent assay kit (Alpco Diagnostics, Salem, NH) and following the manufacturer's guidelines.

Calculation of results

A standard curve was constructed from the standards to determine the level in each sample. A 4-Parameter Logistic (4-PL) curve fit with 1/y2 weighting was used for data analysis. The sample concentration was multiplied by 5000 to obtain the value of HMW and total adiponectin in the sample.

Ethical approval: This study obtained its approval from the Institutional Review Board, Faculty of Medicine, Mansoura University (Code Number: MS. 21.10.1701). Confidentiality and privacy were maintained during the study. Patients were free to withdraw at any time with no consequences. Data were not utilized for any other purpose. A written consent was taken from each participant prior to participation, with explanation of the purpose and methods of the study. The Helsinki Declaration was followed throughout the study's conduction.

Statistical analysis

Data were analyzed by the SPSS V 22 for Windows®. They were tested for normality by Shapiro Walk test. Qualitative data were expressed as numbers and relative percents. Difference between qualitative variables was calculated by chi square test (χ^2) and Fisher exact test. Quantitative data were represented as means ± SD. Independent samples t-test was utilized for comparison between 2 independent groups of parametric data and Mann Whitney U test was utilized for non-parametric data. Spearman's correlation was utilized to test for association between 2 variables with non-parametric quantitative data. The significance level (p-value) was judged at ≤ 0.05.

RESULTS

As shown in table **(1),** the mean age of cases was 46.85 ± 12.48 years versus 46.38 ± 9.91 years in controls, without significant difference (p = 0.093) among both groups. Woman represented the higher % of the participants in both groups and represented 70% in the cases group and 75% in control group, without significant difference between both groups (p = 0.572). The mean BMI in the patients' group was 27.02 ± 2.58 kg/m^2, while in controls was 27.37 ± 2.75 kg/m^2, without significant difference among both groups. Concerning laboratory investigations in the 2 groups, hemoglobin level, hematocrit value and platelets count were statistically significantly lower among RA cases in comparison with controls.

The ESR was statistically significantly higher among RA cases in comparison with controls. Rheumatoid factor was positive in 82.5% of the cases in RA while it was positive in 22.5% in controls, with high significant difference among both groups (p < 0.001). Anti-CCP antibodies were positive in 27.5% of the cases while it was negative in all controls, with high significant difference between both groups. Other laboratory parameters didn't reveal any significant difference among both groups. The median (IQR) concentration of HMW-APN in the cases group was 311.43 (114.64-475.97) Pg/ml whereas in controls, it was 64 (46.37-93.36) Pg/ml. The serum level of HMW-APN was significantly greater among RA cases versus controls.

Table (1): Demographics, BMI, laboratory analysis and HMW-APN in RA cases and control subjects

		RA group (N=40)		Control group (N=40)		Test of significance	P Value
Age (years)		46.85 ± 12.48		46.38 ± 9.91		t= -1.702	P = 0.093
Sex	Males	12	30%	10	25%	χ2= 0.251	P= 0.617
	Females	28	70%	30	75%		
BMI (kg/m^2)		27.02 ± 2.58		27.37 ± 2.75		t= -0.964	P= 0.572
Laboratory analysis							
Haemoglobin (gm/dl)		9.22 ± 2.24		10.41 ± 1.60		t= - 2.735	0.004*
RBCs (106/ml)		3.86 ± 0.93		4.17 ± 0.75		t= - 1.660	0.101
Haematocrit (%)		29.51 ± 7.16		32.59 ± 6.38		t= - 2.027	0.046*
MCV (femtoliters/cell)		78.49 ± 7.25		78.77 ± 6.76		t= - 0.176	0.861
MCH (picograms/cell)		25.07 ± 3.06		25.12 ± 2.99		t= - 0.069	0.945
MCHC (gm/dl)		31.75 ± 2.99		31.02 ± 2.13		t= 0.248	0.722
WBC count (106/ml)		6.4±1.4		7±1.5		z= 1.097	0.273
Neutrophil count (106/ml)		57.37 ± 12.05		56.29 ± 11.37		t= 1.206	0.230
Lymphocyte count (106/ml)		30.15 ± 11.74		31.24 ± 11.27		t= - 1.053	0.360
PLTs(106/ml) /µl)		224± 54		312.5 ±26.1		z= - 2.926	0.003*
Serum creatinine (mg/dl)		0.81 ± 0.18		0.82 ± 0.18		t= - 0.252	0.802
Serum bilirubin (mg/dl)		0.80 ± 0.19		0.76 ± 0.15		t= 0.736	0.622
ALT (U/L)		21.60± 5.15		19.69± 4.60		t= 1.354	0.243
AST (U/L)		18.69± 4.60		21.60±5.15		t= 1.508	0.326
ESR (mm/h)		104.85±24.16		9.55 ± 1.69		t= 30.884	< 0.001*
CRP (mg/dl)		8 ± 1.8		4 ±0.93		z=1.433	0.258
Rheumatoid factor							
Negative		7 (17.5%)		31 (77.5%)		χ2= 28.872	< 0.001*
Positive		33 (82.5%)		9 (22.5%)			
Anti- CCP antibodies							
Negative		29 (72.5%)		40 (100%)		χ2= 12.745	< 0.001*
Positive		11 (27.5%)		0 (0%)			
HMW-APN							
Median (IQR)		311.43 (114.64-475.97)		64 (46.37-93.36)		z = -5.899	< 0.001*

*: statistically significant (P< 0.05).

As shown in in table **(2),** mean disease duration in the cases group was 8 ± 3.88 years. The mean Duration of morning stiffness was 99.03 ± 44.31 minutes. The median number of the tender joints was 4 joints with IQR between 2 and 6 joints. The median number of the swollen joints was 2 joints with IQR between 1 and 4 joints. The table also showed that the median Larsen grading scale was 21 with IQR between 11 and 34. Regarding the extra-articular manifestations among the cases group, gastritis was the commonest manifestation (85%), then rheumatoid nodules in 42.5% and pleurisy in 27.5% of the cases. Other symptoms included carpal tunnel syndrome in 25%, interstitial lung diseases (ILD) in 7.5%, sicca symptoms in 20%, Raynaud's phenomenon in 5% and cutaneous vasculitis in 12.5%. The mean DAS28-ESR score in the included cases was 4.6 ± 0.74. According to the DAS28-ESR score, the cases were classified into three grades of activity, low activity in 4 cases (10%), moderate activity in 28 cases (70%) and high disease activity in 8 cases (20%).

Table (2): Clinical and imaging data and disease activity score of RA cases

		RA cases (N=40)
Disease duration (Years)	Mean ± SD	8 ± 3.88
Duration of morning stiffness (Minutes)	Mean ± SD	99.03 ± 44.31
No. of tender joints	Median (IQR)	4 (2 -6)
No. of swollen joints	Median (IQR)	2 (1 -4)
Larsen grading scale	Median (IQR)	21 (11 -34)
Extra-Articular manifestations of RA		
Rheumatoid nodules		17 (42.5%)
Carpel tunnel syndrome		10 (25%)
Pleurisy		11 (27.5%)
Interstitial lung diseases (ILD)		3 (7.5%)
Sicca symptoms		8 (20%)
Gastritis		34 (85%)
Raynaud's phenomenon		2 (5%)
Cutaneous vasculitis		5 (12.5%)
DAS28-ESR score	Mean ± SD	4.6 ± 0.74
RA disease activity		
Low activity	4 (10%)	
Moderate activity	28 (70%)	
High activity	8 (20%)	

Table **(3)** shows that serum HMW-APN was significantly higher in RA cases with high disease activity in comparison with those with low and moderate disease activity.

Table (3): Analysis of HMW-APN in RA cases as regards disease activity using DAS28-ESR

	Low Activity (N=4)	Moderate Activity (N=28)	High Activity (N=8)	Test of Significance	P value
Serum HMW-APN (Pg/ml)					
Median (IQR)	87.69 (65.88-106.20)	274.77 (139.41-443.04)	574.19 (401.55-835.90)	KW = 12.939	0.002* P1= 0.106 P2<0.001* P3<0.001*

Median and IQR: non parametric test. *: statistically significant (P< 0.05) P1: Significance between the RA cases with low disease activity versus RA with moderate disease activity. P2: Significance between the RA cases with low disease activity versus RA with high disease activity. P2: Significance between the RA cases with moderate disease activity versus RA with high disease activity.

In table **(4),** a significant positive relationship existed between HMW-APN with number of swollen joints and DAS28-ESR score, ESR, rheumatoid factor and anti-CCP antibodies. A significant positive correlation existed between HMW-APN with Larsen grading scale.

Table (4): Association of serum HMW-APN (Pg/ml) with clinical and laboratory data and Larsen grading scale in RA group

		HMW-APN
Age (years)	r_s:	-0.167
	P	0.304
BMI (kg/m^2)	r_s:	0.120
	P	0.463
Disease duration	r_s:	-0.142
	P	0.381
Duration morning stiffness	r_s:	0.043
	P	0.795
No. of Tender joints	r_s:	0.266
	P	0.097
No. of swollen joints	r_s:	**0.348**
	P	**0.028***
DAS28-ESR	r_s:	**0.340**
	P	**0.032***
Haemoglobin (gm/dl)	r_s:	0.098
	P	0.546
RBCs (10^6/ml)	r_s:	-0.014
	P	0.931
TLC	r_s:	-0.166
	P	0.307
Platelets (10^6/ml) /µl)	r_s:	-0.032
	P	0.846
ESR (mm/h)	r_s:	**0.359**
	P	**0.023***
CRP (mg/dl)	r_s:	-0.110
	P	0.498
Rheumatoid factor	r_s:	**0.388**
	P	**0.013***
Anti-cyclic citrullinated peptides (CCP) antibodies	r_s:	**0.429**
	P	**0.006***
Larsen Grading Scale	r_s:	**0.332**
	P	**0.036***

r_s: Spearman's correlation, P: Probability, *: Statistically significant ($p \leq 0.05$).

Table **(5)** displayed that the best cutoff point of serum HMW-APN to identify RA from healthy control was > 77.04 Pg/ml. This point showed high sensitivity (87.5%) with moderate specificity (70%) and AUC (0.883).

Table (5): Predictive value of serum HMW-APN in identifying RA patients.

Diagnostic criteria	Serum HMW-APN (Pg/ml)
AUC	0.883
Cut off point	> 77.04
95% CI	**0.746-0.972**
Sensitivity	**87.5 %**
Specificity	**70 %**
PPV	**72.4 %**
NPV	**82.5 %**
Accuracy	**85.2 %**
*: Statistically significant ($p \leq 0.05$)	

Table **(6)** showed that, in the RA group, the cases with positive rheumatoid nodules had significantly greater HMW-APN concentrations versus cases with absent nodules. No significant difference was reported as regards the existence or absence of other manifestations.

Table (6): Association of serum HMW-APN (Pg/ml) according to the symptoms and signs in the RA group

Variables	Serum HMW-APN level	Test of significance	P value
Rheumatoid nodules			
Absent (n= 23)	222.8 (53.42 – 555.78)	z = - 2.175	**0.030***
Present (n= 17)	381.16 (41.86 – 1000)		
Carpel tunnel syndrome			
Absent (n= 30)	248.98 (41.86 – 856.97)	z = - 1.249	0.212
Present (n= 10)	448.03 (60.67 – 1000)		
Pleurisy			
Absent (n= 29)	331.06 (41.86 – 1000)	z = - 0.379	0.705
Present (n= 11)	254.8 (58.96 – 555.78)		
ILD			
Absent (n= 37)	294.74 (41.86 – 1000)	z = - 0.693	0.488
Present (n= 3)	381.16 (215.71 – 592.61)		
Sicca syndrome			
Absent (n= 32)	274.77 (41.86 – 1000)	z = - 0.345	0.398
Present (n= 8)	354.64 (60.67 – 856.97)		
Gastritis			
Absent (n= 6)	309.18 (41.86 – 770.7)	z = - 0.492	0.622
Present (n= 34)	311.43 (53.42 – 1000)		
Raynaud's phenomenon			
Absent (n= 38)	311.43 (41.86 – 1000)	z = - 0.062	0.951
Present (n= 2)	291.2 (79.64 – 502.76)		
Cutaneous vasculitis			
Absent (n= 35)	328.12 (41.86 – 1000)	z = - 0.716	0.474
Present (n= 5)	243.16 (78.08 – 405.86)		

Data are presented as median (IQR) *: Statistically significant ($p< 0.05$).

DISCUSSION

RA is a systemic autoimmune disease characterized mainly by inflammatory arthritis and musculoskeletal disorders [12]. In RA, synovial hyperplasia, lymphocytic infiltration and aberrant proliferation of fibroblast-like synoviocytes are the main features. These features eventually cause erosive joint damage [13]. Rheumatoid factor has been a primary diagnostic test; but with only 75% sensitivity and limited specificity as it is also present in other autoimmune disorders, infectious diseases and to a certain extent in the healthy people [14]. APN is released predominately by adipose tissue but also by other cells, such as skeletal muscle cells and cardiac myocytes [15]. Adiponectin is present in plasma in large quantities, representing 0.01% of total plasma proteins [16]. The likely role of adiponectin in RA was widely studied, however with conflicting data. Therefore, our study aimed at the assessment of serum concentration of HMW-APN in RA patient and its association with disease activity.

In the current study, regarding the extra-articular manifestations among the cases group, gastritis was the commonest manifestation (85%), then rheumatoid nodules in 42.5% and pleurisy in 27.5% of the cases. Other symptoms included carpal tunnel syndrome in 25%, interstitial lung diseases (ILD) in 7.5%, sicca symptoms in 20%, Raynaud's phenomenon in 5% and cutaneous vasculitis in 12.5%. The current results agree with **Khater and Al Sheik** [17] who reported that subcutaneous nodules and ILD were found only in rheumatoid patients, represented as presented by 1 and 2, respectively.

Regarding the disease activity in the current study, according to DAS28-ESR, there were low activity in 4 cases (10%), moderate activity in 28 cases (70%) and high disease activity in 8 cases (20%). This is in agreement with **Senousy *et al***. [18] who studied 94 patients with RA, 52.5% of RA cases showed a mild/high disease activity score for DAS28-ESR, with 79%, 66%, 21%, and 23.5% of cases had joint inflammation, deformities, rheumatoid nodules, and extra-articular manifestations, respectively. In contrast, **Shaker and his colleagues** [19] showed that according to DAS28-ESR, low disease activity was reported in 54% and moderate to high activity was detected in 46% [19].

In our work, serum HMW-APN levels were significantly greater ($p< 0.001$) among RA cases in comparison with controls. This is in agreement with **Chen *et al.*** [20] who reported that APN had a negative association with disease activity and Sharp score in 125 Chinese RA cases. They showed that the mean serum APN in RA cases (25.0 ± 19.1 µg/mL) was significantly higher than in healthy controls (13.6 ± 5.5 µg/mL). However, this disagrees with **Lei *et al***. [21] who included 60 RA cases (49 females and 11 males) and the results demonstrated that APN concentrations in RA cases were lower compared to concentrations in controls ($P = 0.007$).

In our work, serum HMW-APN was significantly higher among cases with high disease activity in comparison with the cases with low and moderate disease activity. Also, a significant positive association was found between HMW-APN with number of swollen joints and with ESR. This agrees with **Khajoei *et al***. [22] who reported that APN levels were 8.5 µg/mL, 10.75 µg/mL, 14.25 µg/mL, and 15 µg/mL in remission, mild, moderate and severe groups, respectively. This is in consent with the cross-sectional study by **Minamino *et al.*** [23] in which serum APN levels in Japanese RA cases under treatment showed significant association with higher DAS28-ESR.

In our work, a significant positive relationship existed between HMW-APN with Larsen grading scale ($r= 0.332$, $p= 0.036$). Conflicting results on RA have been found, such as that high APN levels in synovial membrane induce inflammatory cytokines and MMPs [24, 25]. The current results agree with **Lei *et al.*** [21] who found that cases having severe synovial thickening had higher APN levels. The current results also come in agreement with many studies reporting a significant relationship between APN concentrations in the serum and radiographic joint damage [26-28]. The explanation for the positive correlation is because the RA is a systemic disorder, yet the synovial membrane still have an essential role. The intimal lining structure of synovial membrane includes macrophage-like and fibroblast-like synoviocytes. With the onset of RA, this lining significantly expands due to activation of such cell types. Macrophage-like synoviocytes can release several cytokines, e.g. IL-6 and TNF. For fibroblast-like synoviocytes, apart from IL-6, they can also release large quantities of MMPs and prostaglandins [29].

In the current work, the best cutoff point of serum HMW-APN to identify RA from healthy control was > 77.04 Pg/ml. This point showed high sensitivity (87.5%) with moderate specificity (70%) and AUC (0.883). Up to our knowledge, no previous studies have reported the cutoff point to identify RA by measurement of serum adiponectin. This is the main strength point as it could give us a clue for early disease diagnosis by this less invasive measurement.

Limitations: The sample size and being a single center study are the main limitations that could decrease the power of the obtained results. Also, this was a cross-sectional study with no longitudinal data, and its results do not indicate causation. The long-term effect of treatment drugs on serum APN remains unidentified, and the pathophysiologic role of APN in RA progression necessitates more investigations.

CONCLUSION

We concluded that RA is common rheumatological disorder that influence the daily quality of life in the affected patients with high burden on the subjects and the community. Serum HMW-APN levels could be used as reliable biomarker in diagnosis of rheumatoid arthritis in addition to determination of disease activity.

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