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Fatima Qasim AL-Obaidy
Department of Applied Science, Branch of Applied Chemistry, University of Technology, Baghdad, Iraq,
tamtamfeef91@gmail.com

Abdulnasser M. Al-Gebori
Department of Applied Science, Branch of Applied Chemistry, University of Technology, Baghdad, Iraq,
abdulnasser.m.abdullah@uotechnology.edu.iq

Mohammed Hadi Munshed Alosami
Department of Medicine, Colleges of Medicine, University of Baghdad, Baghdad, Iraq,
Mohammad_alosami@yahoo.com

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RESEARCH ARTICLE

The Correlation of Anti-Acetylated Peptide Antibodies with Anti-Acetylated Lysine Peptide Antibodies and Anti-Acetylated Ornthinine Peptide Antibodies with Rheumatoid Arthritis

Fatima Qasim AL-Obaidy [1,*], **Abdulnasser M. Al-Gebori** [1], **Mohammed Hadi Munshed Alosami** [2]

[1] Department of Applied Science, Branch of Applied Chemistry, University of Technology, Baghdad, Iraq
[2] Department of Medicine, Colleges of Medicine, University of Baghdad, Baghdad, Iraq

ABSTRACT

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease with a global prevalence of 0.24%–1%, requiring early diagnosis and aggressive treatment. It is associated with synovial and cartilage destruction. This study is designed to investigate the evaluation of anti-acetylated peptide antibodies (AAPA), acetylated lysine peptide antibodies (AcLys,), anti-acetylated ornthinine peptide antibodies (AcOrn), liver function test, and body mass index (BMI) in Rheumatoid arthritis patients. One hundred-ten RA patients (86.36% female, 13.63% male) in comparison with forty healthy controls. Anti-acetylated- peptide Antibodies (AAPA), Anti-acetylated Lysine peptide Antibodies (AcLys), Anti-acetylated-ornthinine peptide Antibody (AcOrn) were determined by Enzyme Linked Immunosorbent Assay (ELISA) and liver function levels were used to measure by spectrophotometer in the serum of RA patients and healthy controls. The mean∓SE of age in patients and healthy controls were 51 0.89 years and 49 1.48 years respectively. According to treatment, the patients of the study were divided into three subgroups [biology treatment (bDMARDs), conventional treatment (cDMARDs) subgroup and combined (DMARDs) subgroup]. The mean SE of AAPA in RA patients and healthy controls were 51.05 5.613 ng/mL and 19.98 3.29 ng/mL respectively. Results showed there was a significant increase between all subgroups of AAPAs ($p < 0.001$), AcOrns ($p < 0.001$) and AcyLs ($p < 0.001$) as compared to healthy control whereas there were no significant differences in AAPA between subgroups with each other's. While AcOrns levels showed a significant increase in chemotherby as compared to biology subgroup ($p < 0.0149$), in addition levels of AcLys showed a significant increase in biology subgroup and biochemistry as compared to chemotherapy subgroups.

Keywords: Anti-acetylated-peptide antibodies, Anti-acetylated lysine peptide antibodies, Alkaline phosphatase, Body mass index, Inflammation, Rheumatoid arthritis (RA), Synovial

Introduction

Rheumatoid arthritis (RA) is among the most important chronic diseases that can cause joint destruction with variable clinical symptoms especially in the adulthood which characterized by mild to severe inflammation of the joints that can result in pain, dryness and joint destruction and disability. [1,2] Age, gender, genetics and contact with the environment are all risk factors for rheumatoid arthritis. [3,4] Autoantibodies against post-translationally changed proteins are a defining feature of rheumatoid arthritis and

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* Corresponding author.
E-mail addresses: tamtamfeef91@gmail.com (F. Q. AL-Obaidy), abdulnasser.m.abdullah@uotechnology.edu.iq (A. M. Al-Gebori), Mohammad_alosami@yahoo.com (M. H. M. Alosami).

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associate with disease progression and various classes of anti-modified protein antibodies (AMPAs) have been identified in RA for various protein modifications like citrullination, carbamylation, and acetylation.[5] Acetylation of lysine residues is a post-translational protein modification (PTM) that is normally mediated by lysine acetyltransferase (Kynurenine aminotransferase isozymes (KATs)) but can also occur non-enzymatically in mitochondria that it may play an important role in the pathophysiology of RA by generating antibody response.[6] Cells have 3600 lysine acetylation sites in 1750 proteins, that a key regulatory mechanism, epigenetic processes and regulation of protein stability and interactions in all eukaryotic organisms.[7] At present anti-acetylated protein antibodies (AAPA), Anti-acetylated Lysine peptide Antibodies (AcLys) and Anti-acetylated-ornthinine peptide Antibody (AcOrn) challenged the concept of seronegative RA, putting forward the hypothesis that the diagnostic gap can be closed or at least partially covered.[8] AAPA recognizes epitopes where certain lysine residues have been enzymatically changed to bear an acetyl group. AAPA is common in 35% of individuals with early arthritis, IgG and IgA antibodies and 40% are shown to have pre-existing anti-acetylated protein antibodies (AAPA) against an acetylated vimentin peptide, mostly restricted to the ACPA-positive subgroup.[5] Asymptomatic abnormal liver tests are the most common manifestation of RA-related liver injury.[8] Cirrhosis can develop from liver injury on rare occasions. Patients with RA are more likely to develop an autoimmune liver disease.[9,10] Rheumatology medications are frequently hepatotoxic, and rising levels of cytokines such as interleukins (IL-10, IL-17) can be found in the synovium of RA patients, which play an essential role in chronic liver illnesses and are also related with disease progression.[11,12] Body mass index (BMI)-measured excess body weight has been linked to a number of autoimmune and inflammatory disorders, and adipose tissue is thought to have a role in modulating physiological and pathological processes related to inflammation and immunity.[13]

Materials and methods

A total of 110 RA patients with mean age of patients 51 ± 0.89 years, and the predominant age category was 36–65 years (95 females and 15 males), and 40 healthy controls (28 females and 12 males) matched in age and sex to the patients. Across sectional study was carried out at Rheumatology Consultation Clinic, Baghdad Teaching Hospital between September 15, 2022, and March 25, 2023.Female gender was greater than male gender (86.36% female and 13.7% male), with a female: male ratio of 5:1. Diagnosis, treatment, and follow-up of all patients were performed in this clinic and Young individuals, or individuals with a history of disability, psychological and mental diseases, malignant tumors, autoimmune diseases were excluded from the study. According to the kind of treatment (methotrexate, etanercept, and prednisolone), the patients were divided into three subgroup: (1) biological treatment subgroup (consisted of thirty-eight patients on the bDMARDs treatment), (2) conventional cDMARD subgroup (thirty-eight patients received MTX) and (3) combined DMARD subgroup (thirty-four patients had received biology and chemotherapy).

Venous blood of about 3–5 mL was taken from rheumatoid arthritis patients and control volunteers; it was collected in a gel tube. After centrifugation for 10 minutes at 5000 rpm to separate serum, which was distributed into Eppendorf tubes and kept frozen at –20 °C until analyzed, the serum of RA patients and controls were assessed for the level of AAPA. AcOrns and AcLys using commercially available kits (SunLong Biotech Kit, China) by Sandwich Enzyme-Linked Immunosorbent Assay (ELISA) (Biorad,Germany) Liver function tests (ALT, AST, and ALP) were carried out by commercial kits (Biolab, USA) and measured by a spectrophotometer (CECELL 3000). The study collected venous blood from rheumatoid arthritis patients and control volunteers. The serum was analyzed for AAPA, AcOrns, AcLys, and liver function tests (ALT,AST,ALP). The BMI was calculated using the equation BMI = [weight/height2 (kg/m^2)].

Statistical analysis

The data was analyzed using SPSS-V26, with parametric data provided as means ± standard error. Age, gender, and differences between patients and control were compared using independent samples T test. Serum AAPAs, AcOrns, AcLys, and liver function test levels were compared between RA subgroup patients and healthy control. The level of statistical significance was calculated at 0.05.

Results and discussion

In this study, 110 RA patients (95 female and 15% male,) were compared to 40 healthy controls. Patients ranged in age from 50 to 59 years old on average. Female gender outnumbered male gender (5:1) are shown in Table 1.

Table 1. Demographic characteristics of RA patients.

Characteristics	Patients n = 110 Mean (min-max)
Age (years)	51 (36–75)
BMI(kg/m^2)	32 (22–47)
ALT(U/L)	23 (5–147)
AST(U/L)	23 (9–112)
ALP (IU/L)	110 (36–204)
Gender	
Male	15 (13.7%)
Female	95 (86.36%)
Treatment	
Biology	38 (34.5%)
Chemotherapy	38 (34.5%)
Biochemotherapy	34 (30.9%)

ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, BMI: Body mass index ALP: Alkaline phosphates.

Table 2 summarizes all anthropometric information collected from patients and controls; the age range was (51 ± 0.89) and (49 ± 1.48) for patients and controls, respectively. Body mass index measurements show a high significant difference (P = 0.0005) between patients (32.9 ± 0.45) and the control group (30 ± 0.6). Whereas there were highly significant differences in [ALT (P = 0.02), AST (P = 0.02), and ALP (P = 0.0001)] levels in RA patients in comparison to healthy controls.

Table 2. Comparisons of multiple parameters between RA patients and healthy control.

Parameters	Healthy control mean ± SE	RA Patients mean ± SE	*P*-value
Age (years)	49 ± 1.480	51 ± 0.89	0.23
BMI (kg/m^2)	30 ± 0.610	32.9 ± 0.45	0.0005**
ALT (U/L)	16.01 ± 0.91	22.9 ± 1.89	0.02**
AST (U/L)	17.6 ± 0.65	23 ± 1.430	0.02**
ALP (IU/L)	80.71 ± 3.5	110 ± 3.50	0.0001**

*Significant at $P \leq 0.05$.
**High Significant at P ≤ 0.001.
BMI: Body mass index, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase. ALP: Alkaline phosphates-value: Probability value, SE: standard error, mg/dl: milligrams per deciliter, U/L: unites per litter, IU/L: international units per litter.

Table 3 showed a highly significant increase in, [AAPA ($p = 0.0015$) AcLys ($p = 0.0001$) and AcOrn ($p = 0.004$)] in patients of RA in compare with healthy control.

Statistical analysis of AAPAs levels distributed among RA patients subgroup and control showed that the mean ± SE of AAPA in healthy controls (9.29 ± 1.19) ng/mL, biology (26.31 ± 5.69) ng/mL, chemotherpy (22.31 ± 5.11) ng/mL and biochemotherpy (20.56 ± 9.24) ng/mL as shown in Table 4.

Table 3. Levels of autoantibodies in the sera of RA patients and healthy control.

Parameters	Healthy control Mean ± SE	Patients Mean ± SE	*P* value
AAPA (ng/mL)	9.29 ± 1.19	23.07 ± 3.950	0.0015**
AcLys (ng/mL)	20.3 ± 3.53	77.27 ± 19.37	0.0001**
AcOrn (ng/mL)	10.72 ± 1.25	25.86 ± 4.070	0.004**

*Significant at $P \leq 0.05$.
**High Significant at $P \leq 0.001$.
AAPA: anti-acetylated peptide antibodies AcLys: anti-acetylated lysine peptide antibodies, AcOrn: anti-acetylated ornithinine peptide antibodies.

Table 4. Serum human AAPA levels in RA patient's groups in comparison with healthy control.

AAPA (ng/mL)			
HC Mean ± SE	Biology Mean ± SE	Chemotherapy Mean ± SE	Biochemotherapy Mean ± SE
9.29 ± 1.19	26.31± 5.69	22.31± 5.11	20.56± 9.24

AAPAs: anti-acetylated peptide antibodies, SE: Standard error, ng/mL: Nanograms per milliliter.

Table 5 shows significant changes in AAPA levels among RA subgroup patients, including biology, chemotherapy, and biochemotherapy, compared to healthy controls, with no significant differences observed in multiple comparisons.

Table 5. Multiple comparisons of AAPA levels in RA patients with biology, RA patients with chemotherapy, RA patients with biochemotherapy and healthy control all with each other's.

Parameter	Group treatments	*P* value
AAPA (ng/mL)	HC vs. Biology	0.0001**
	HC vs. Chemotherapy	0.0057**
	HC vs. Bio-chemotherapy	0.0222*
	Biology vs. Chemotherapy	0.7304
	Biology vs. Biochemotherapy	0.4498
	Chemotherapy vs. Biochemotherapy	0.9691

*Significant at P < 0.05.
**Highly Significant at P < 0.01.
AAPAs: anti-acetylated peptide antibodies, HC: healthy control, P-value: probability value, ng/mL: Nanograms per milliliter.

Results of the current study demonstrated that the levels of AcLys in the RA subgroup [biology (92.943 ± 4.93 ng/mL), chemotherapy (54.307 ± 3.86 ng/mL), biochemotherpy (84.572 ± 8.9 ng/mL), and healthy control (20.3 ± 3.53 ng/mL)] were as shown in Table 6.

Table 6. Serum human AcLys levels in RA patient's groups in comparison with healthy control.

AcLys (ng/mL)			
HC Mean ± SE	Biology Mean ± SE	Chemotherapy Mean ± SE	Biochemotherapy Mean ± SE
20.3 ± 3.53	92.943 ± 4.93	54.307 ± 3.86	84.572 ± 8.9

AcLys: anti-acetylated lysine antibodies, HC: healthy control, SE: Standard error, ng/mL: Nanograms per milliliter.

Results in Table 7 showed a significant increase in the levels of AcLys in subgroup patients with RA compared to healthy controls. Whereas multiple comparisons of subgroups with each other showed a highly significant increase in the biology subgroup as compared to the chemotherapy subgroup and a significant increase in the biochemotherapy subgroup compared to the chemotherapy subgroup in patients with RA. Moreover, there is no significant difference between the biology subgroup compared to biochemotherapy subgroup.

Table 7. Multiple comparisons of AcLys levels in RA patients with biology, RA patients with chemotherapy, RA patients with biochemotherapy and healthy control all with each other's.

Parameter	Group treatments	*P* value
AcLys (ng/mL)	HC vs. Biology	0.0001**
	HC vs. Chemotherapy	0.0127**
	HC vs. Bio-chemotherapy	0.0002**
	Biology vs. Chemotherapy	0.0061**
	Biology vs. Biochemotherapy	0.7351
	Chemotherapy vs. Biochemotherapy	0.0236*

**Highly Significant at P ≤ 0.01 AcLys: anti-acetylated lysine peptide antibodies, HC: healthy control, P-value: probability value, ng/mL: Nanograms per milliliter.

Results demonstrated that the levels of AcOrn in RA subgroup [biology 20.51 ± 3.22 ng/mL, chemotherpy 31.08 ± 7.98 ng/mL and biochemotherpy 25.01 ± 4.32 ng/mL] higher than AcOrn level in the healthy control group 10.72 ± 1.25 ng/mL as shown in Table 8.

Table 8. Serum human AcOrn levels in RA patient's groups in comparison with healthy control.

AcOrn (ng/mL)			
HC	Biology	Chemotherapy	Biochemotherapy
Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
10.72 ± 1.25	20.51 ± 3.22	31.08 ± 7.98	25.01 ± 4.32

AcOrn: anti-acetylated ornithine antibodies, HC: healthy control, SE: Standard error, ng/mL: Nanograms per milliliter.

Results in Table 9 revealed a substantial significant increase in serum AcOrn levels between biology in comparison to HC (p = 0.0281), chemotherapy in comparison to HC (p = 0.0001) and combined biochemtherpy as compared to HC (p = 0.004). Multiple comparisons between subgroups showed significant decrease of biology subgroup as compared with chemotherapy subgroup, whereas no significant difference between others group with each other's.

In RA, Pearson's correlation was utilized to examine the possible correlation between AAPA and (AcLys, AcOrn, age, BMI,ALT,AST,and ALP). Results showed a significant negative correlation between AAPA and BMI (R = –0.418, P = 0.05*) in the biochemotherpy subgroup, whereas no significant correlation between AAPA with other parameters in different subgroups of RA patients as shown in Table 10 and Fig. 1.

Table 9. Multiple comparisons of AcOrn levels in RA patients with biology, RA patients with chemotherapy, RA patients with biochemotherapy and healthy control all with each other's.

Parameter	Group treatments	P value
AcOrn (ng/mL)	HC vs. Biology	0.0281*
	HC vs. Chemotherapy	0.0001**
	HC vs. Bio-chemotherapy	0.0004**
	Biology vs. Chemotherapy	0.0149*
	Biology vs. Bio-chemotherapy	0.5658
	Chemotherapy vs. Bio-chemotherapy	0.3022

*Significant at P ≤ 0.05.
**Highly Significant at P ≤ 0.01.
Anti-acetylated ornithine antibodies (AcOrn), HC: healthy control, ng/mL: Nanograms per milliliter.

Discussion

Results in the current study revealed a high significant increase in BMI in RA patients due to that obesity in RA patients significantly clinically symptoms, inflammation markers, outcomes and chronic pain and it is believed to be associated with a number of chronic illness.[14,15] The results corroborate with other studies done in RA Iraq patients by Haitham Ahmed et al.,[16] and another study of Younis and, Al-Bustany,[17] which reported There was increased frequency of obesity in rheumatoid arthritis patients and a significant relationship between fibromyalgia syndrome (FMS) with obesity.[16,17] Another Iraqi study showed a significant relationship between FMS and increased BMI.[18] the explanation of these findings obese people's adipose tissue secretes inflammatory cytokines such as Tumor necrosis factor-β (TNF-β), interleukin-1(IL-1), and Individuals' inflammatory responses are triggered by these adipokines.[19] Moreover, patients with RA take hydrocortisone during the course of treatment to inhibition the level of inflamed joints and others site in body.[20] Result in current study showed that there was a substantial rise in the activity of aminotransferases AST (p = 0.02) and ALT (p = 0.02) when compared to the healthy control. This results consist with other study by Alexander et al.[21] and by tawfeeq HR., and Ali[11] in Iraq which reported that patients with RA are more likely to develop an autoimmune liver disease due to Rheumatology medications are frequently hepatotoxic, and rising levels of cytokines such as interleukins (IL-10, IL-17) can be found in the synovium of RA patients, which play an essential role in chronic liver illnesses and are also related with disease progression.[11,21] ALP levels increased significantly in RA

Table 10. The correlation between AAPA and other parameters in studied group treatments.

AAPA vs Parameters	Biology		Chemotherapy		Biochemotherapy	
	R	P-value	R	P-value	R	P-value
ACLYS (ng/ml)	0.030	0.89	–0.141	0.55	–0.041	0.54
ACORN (ng/ml)	–0.217	0.33	–0.042	0.84	0.034	0.87
Age (years)	0.239	0.28	0.022	0.92	–0.102	0.65
BMI (kg/m^2)	0.067	0.74	–0.162	0.47	–0.418	0.05*
ALT (U/L)	–0.105	0.64	–0.169	0.45	0.091	0.68
AST (U/L)	–0.094	0.67	–0.105	0.64	0.063	0.78
ALP (IU/L)	–0.070	0.75	–0.078	0.73	0.083	0.71

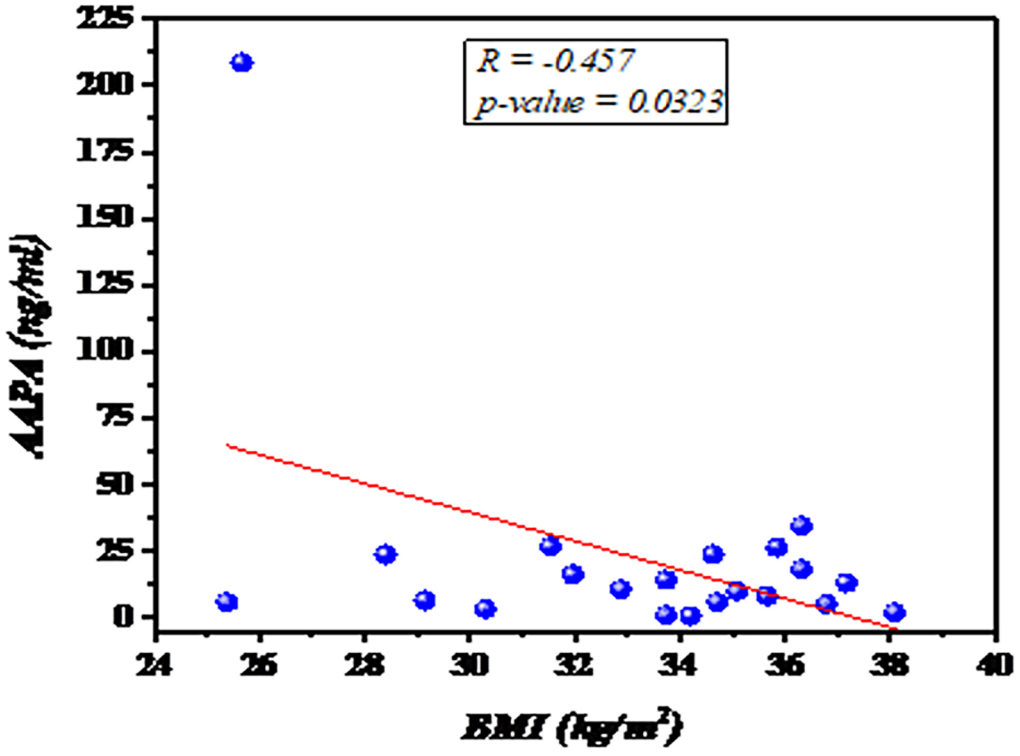

Fig. 1. Scatter plot shows the correlation between AAPA and BMI in RA biochemotherpy subgroup.

patients compared to healthy controls. The results are in agreement with a previous study by Joanna Podgórska, who found increased ALP in patients with RA from 18 to 50%.[22] Increased liver enzymes may be caused by drug-induced liver disorders, particularly methotrexate, which affects 45% of RA patients, especially ALP and albumin.[23] Lysine acetylation is a common protein post-translational modification (PTMs).[24] Two peptides for AAPA detection (AcLys and AcOrn) and investigated their correlation with BMI and liver function test in RA patients and healthy control. Result in current study showed increased concentration of AAPA, Aclys and Acorn in patients of RA. These results conducted with previous study by Paul Studenic et al.[25] which reported that AAPA prevalent in early RA, independently of RF and ACPA, reducing seroreactivity gap.[25] The current study found a high significant AAPA level in biology subgroups of RA patients compared to healthy control, indicating pathogenic B cells. This dominance suggests activity in RA, with at least five dominant BCR clones in peripheral blood leading to severe symptoms.[26] Data analysis of this study found significant differences in AcLys seroprevalence among RA patients and healthy controls, with biology and chemotherapy subgroups showing significant differences compared to the chemothepy subgroup, while biology and biochemotherpy subgroups showed no significant differences. These findings are consistent with previous studies that found the mechanism MTX impairs B cell development, reduces cytokines like Tumor necrosis factorα- (TNF-α) and interleukin -6(IL-6), which are secreted by T cells, and improves response to AAPA, reducing autoantibody titers in

RA.[27–29] The current study showed a significant increase in serum AcOrn levels among RA subgroup treatments, with the biology subgroup showing a decrease compared to chemotherapy and no significant difference between groups. The explantation of the finding due to a 19:3 female-to-male ratio in our study, attributed to two factors: stronger female immune systems and hormonal changes during pregnancy and menopause. This may be linked to female patients having easier access to clinical data.[30,31] AAPA levels significantly inversely correlated with BMI in RA patients' biochemotherpy subgroup. BMI plays a different role in these two major RA subsets depending on the presence of ACPA. However, the high heterogeneity may indicate a shift in the connection between BMI and ACPA seropositivity or seronegativeness.[32] In biochemotherpy subgroup the patient received MTX plus TNFi is a beneficial treatment for some RA patients due to proinflammatory adipokines and decreased antibody levels. Obesity is linked to RA development in women and inversely related to RA in men, but not remission.[33–35]

Conclusion

Rheumatoid arthritis requires early intervention for treatment and diagnosis. Anti-acetylated peptide antibodies improve classification in RA patients without RF and anti-CCP. Inflammatory arthritis patients often experience liver function abnormalities due to DMARDs. Obesity negatively impacts disease improvement in RA patients.

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Authors' contributions

M. H.M participated in specifying the title of the research and also diagnosing patients according to disease-specific criteria of this study. A. M.A participated in specifying the title of the research and study the variation of parameters and their relationship with disease. F. Q. A collected specimens and prepared the samples to work also determined levels of all parameters using many approaches in many devices as well as conducting a statistical study for research.

Authors' declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images that are not ours have been included with the necessary permission for republication, which is attached to the manuscript.
- No animal studies are present in the manuscript.
- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee at University of technology.

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علاقة الأجسام المضادة للببتيد الأسيتيل مع الأجسام المضادة لببتيد اللايسين المضاد للأسيتيل والأجسام المضادة لببتيد الأسيتيل الأورنثينين بالتهاب المفاصل الرثوي.

فاطمة قاسم العبيدي[1]، عبدالناصر محمد الجبوري[1]، محمد هادي منشد العصامي[2]

[1] *فرع الكيمياء التطبيقية، قسم العلوم التطبيقية، الجامعة التكنولوجية، بغداد، العراق.*

[2] *قسم الطب، كلية الطب، جامعة بغداد، بغداد، العراق.*

المستخلص

التهاب المفاصل الرثوي هو مرض مناعي ذاتي مزمن ومتقدم مع معدل انتشار عالمي يتراوح بين 0.24% إلى 1%، ويتطلب التشخيص المبكر والعلاج العدواني. ويرتبط بالتدميرالزليلي والغضاريف والأمراض الجهازية. تم تصميم هذه الدراسة لدراسة تقييم AAPA وAcLys وAcOrn واختبار وظائف الكبد (ALT وAST وALP) وDAS-28 ومؤشر كتلة الجسم لدى مرضى التهاب المفاصل الرثوي، علاوة على ربط AAPA بمعلمات أخرى. مائة وعشرة مرضى التهاب المفاصل الروماتويدي (86.36% إناث، 13.63% ذكور) مقارنة بأربعين من الأصحاء. تم تحديد الأجسام المضادة للببتيد الأسيتيل (AAPA)، والأجسام المضادة لببتيد الايسين الأسيتيل (AcLys)، والأجسام المضادة لببتيد الأسيتيل الأورنثين (AcOrn) بواسطة مقايسة الامتصاص المناعي المرتبط بالإنزيم (ELISA) وتم قياس مستويات وظائف الكبد (ALT، AST.ALP) بواسطة مقياس الطيف الضوئي في مصل مرضى التهاب المفاصل الرثوي والأصحاء. وكان متوسط العمر في المرضى والأصحاء 51 0.89 سنة و 49 1.48 سنة على التوالي. وفقًا للعلاج، تم تقسيم مرضى الدراسة إلى ثلاث مجموعات فرعية [العلاج البيولوجي (bDMARDs)، المجموعة الفرعية للعلاج التقليدي (cDMARDs) والمجموعة الفرعية المدمجة (DMARDs). كان متوسط SE لـ AAPA في مرضى التهاب المفاصل الروماتويدي والضوابط الصحية 51.05 • 5.613 نانوجرام/مل و19.98 • 3.29 نانوجرام/مل على التوالي. أظهرت النتائج وجود زيادة معنوية بين جميع المجموعات الفرعية لـ (p<0.001) AcOrns، (p<0.001) AAPA و(p<0.001) AcyLs مقارنة بالاصحاء بينما لم تكن هناك فروق ذات دلالة إحصائية في AAPA بين المجموعات الفرعية مع بعضها البعض. في حين أظهرت مستويات AcOrns زيادة كبيرة في العلاج الكيميائي مقارنة بالمجموعة الفرعية للبيولوجيا (P <0.0149)، اضافه الى مستويات AcLys أظهرت زيادة كبيرة في المجموعة الفرعية للبيولوجيا والعلاج الكيميائي الحيوي مقارنة بمجموعات العلاج الكيميائي الفرعية.

الكلمات المفتاحية: الاجسام المضادة لببتيد الاسيتيل، الاجسام المضادة لببتيد اللايسين، الفوسفات القلوي، مؤشر كتلة الجسم، الالتهاب، التهاب المفاصل الروماتويدي، الزليلي.