

Assessment of Liver Enzymes Activity in Patients with Rheumatoid Arthritis in Nineveh province

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Abstract

Aim of the study: to determine the effect of Rheumatoid Arthritis(RA) on liver enzymes level. Methods: 75 subjects were enrolled in this study (40 patients with Rheumatoid arthritis (RA) and 35 healthy subjects as control group), at Mosul city, Northern of Iraq, aged 20-70 years. The biochemical parameters measured were some of liver function tests which include measurement of the liver enzymes activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT). Results: There was a significant increase in liver enzymes activity in patients when compared to control. There was also significant increase in serum AST level at age group 40-50 years when compared to other age group in patients, in addition, there was a significant increase in serum ALP in female patients when compared to male patients. There was non-significant change in liver enzymes activity when compared according to residence, according to family history, and according to rheumatoid factor in patients. Conclusion: The results of the present study indicated no deterioration in liver functions in patients with rheumatoid arthritis regarding serum enzymes (aspartate transaminase, alanin transaminase, gamma glutamyl transferase and alkaline phosphatase), although subclinical alteration in liver functions could be expected in those patients, so that measurement of other early markers of liver dysfunction is occasionally recommended.

Key words: Rheumatoid arthritis, Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and gamma glutamyl transferase.

تقييم فعالية أنزيمات الكبد في المرضى المصابين بالتهاب المفاصل الرثواني في محافظة نينوى

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الخلاصة

هدف البحث: تحديد تأثير مرض التهاب المفاصل الرثواني على مستوى انزيمات الكبد . طرق البحث: 75 شخص شملوا في هذه الدراسة 40 من المصابين بالتهاب المفاصل الرثواني و 35 شخص كمجموعة ضابط ، في مدينة الموصل وضواحيها، شمال العراق، تراوحت اعمارهم بين 20-70 سنة، تم اجراء بعض فحوصات وظائف الكبد عليهم والتي شملت قياس فعالية انزيمات الكبد والمتضمنة مسنوى خميرة ناقلة امين الاسباراتات (AST)، ناقلة امين الالنين (ALT)، الفوسفاتيني القلوية (ALP) وناقل الغاما غلوتاملي (GGT). النتائج: أظهرت الدراسة زيادة معنوية في معدل مستويات انزيمات الكبد (ناقلة امين الاسباراتات، ناقلة امين الالنين، الفوسفاتيني القلوية وناقل الغاما غلوتاميل في مصل الدم لدى المرضى عند مقارنتهم

بمجموعة الضبط بالإضافة إلى زيادة معنوية في معدل مستوى ناقلة امين الأسبارتات عند المرضى الذين تتراوح اعمارهم بين 40-50 سنة وكذلك كان هناك زيادة معنوية في معدل مستوى الفوسفاتيني القلوية لدى المرضى الاناث عند مقارنتهم بالمرضى الذكور . كما أظهرت عدم وجود اختلافات معنوية في معدلات مستويات انزيمات الكبد لدى المرضى عند مقارنتهم طبقاً للسكن، وجود المرض في العائلة، وطبقاً لوجود العامل الرثوي في العائلة . الخلاصة: تبين نتائج الدراسة الحالية عدم وجود اضطرابات ظاهرية في وظائف الكبد لدى مرضى التهاب المفاصل الرثواني بالاعتماد على مستويات انزيمات الكبد في مصل الدم . مع ذلك فانه من المتوقع وحسب النتائج ، وجود تغييرات طفيفة وغير ظاهرة سريريا " في وظائف الكبد لدى هؤلاء المرضى ، وبذلك ينصح بمتابعة وظائف الكبد لدى مرضى التهاب المفاصل الرثواني عن طريق إجراء فحوصات اشمل وأدق لوظائف الكبد.

Introduction

Rheumatoid arthritis (RA), a chronic autoimmune inflammatory disorder of unknown etiology that occurs in approximately 1% of the population^(1,2). In all populations, RA is more prevalent among women than men, and usually develops in the fourth and fifth decades of life, with 80% of the total cases occurring between the ages of 40 and 50⁽³⁾. In RA, joint involvement is typically symmetric, a characteristic usually not found in other forms of arthritis^(3,4). Indeed, the rate of cartilage and joint damage is correlated with plasma elevations in inflammatory acute phase reactants, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)^(5,6,7). No single diagnostic test definitively confirms the diagnosis of rheumatoid arthritis⁽⁸⁾. Baseline laboratory evaluations should include a complete blood cell count (with white blood cell differential and platelet counts), rheumatoid factor (RF) measurement, and measurement of ESR or CRP⁽⁹⁾. Non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoid joint injections, and/or low-dose prednisone may be considered for control of symptoms⁽¹⁰⁾. In light of the therapeutic paradigm shift to early and aggressive treatment, the majority of patients with newly diagnosed RA are started on disease-modifying antirheumatic drug (DMARD) therapy within 3 months of diagnosis⁽¹¹⁾. The liver is often overlooked as a target organ, with pathology either secondary to an underlying disease or due to the toxicity of therapies and the medical

complications of extrahepatic diseases⁽¹²⁾. Although liver involvement is not common in RA, abnormalities in liver tests have been reported in 5% to 77% of patients with RA⁽¹³⁾. Elevated levels of serum aminotransferases have been reported in patients with RA who are not taking systemic therapy and who do not have an alternate diagnosis that explains the increased levels of liver enzymes⁽¹⁴⁾. Abnormal liver tests varying with disease activity, mainly elevated alkaline phosphatase, have been reported in 18 to 50% of patients with RA⁽¹²⁾. The increase in liver isoenzymes has been shown to correlate with RA activity⁽¹⁵⁾. Increases in alkaline phosphatase and g-glutamyl-transpeptidase (GGT) levels are the predominant biochemical abnormality⁽¹⁵⁾. The biochemical abnormalities are typically mild and transient and the histologic abnormalities are non progressive and clinically insignificant⁽¹⁵⁾.

Subjects, Material and Methods

This study represents a case-control study, it presents a data of 75 subjects in Mosul City Northern of Iraq, and they were 64 female and 11 male, aged 20-70 years. The study was conducted over a period of 6 months started from 1st October(2011) until 1st April(2012). The subjects included were divided into 2 groups: Case group, 40 adult patients included 36 females and 4 males, aged 20-70 years with a mean \pm standard deviation (SD) of (47.77 \pm 13.63) of years. They were diagnosed as having RA by rheumatologist according to the 1987 ACR criteria for at least 6 months, collected from

the rheumatology consultant clinic in Ibn-Seena Teaching Hospital, and they do not use any medications for the treatment of RA. The exclusion criteria include subjects with history of liver disease, subjects with diabetes mellitus, pregnancy, subjects with rheumatic disease other than RA, subjects with cardiovascular diseases, alcohol intake and drugs intake which may affect the results of liver function tests. The second, control group include 35 apparently healthy subjects, included 28 females and 7 males, aged 20-70 years with a mean \pm standard deviation (SD) of (46.36 \pm 11.95) years. They were randomly selected from volunteers and companions of other patients. This control group was judged free of any illness by history, they were included in this study to establish the normal values for ALT, AST, GGT, & ALP. All patients were first interviewed and examined clinically in the presence of a rheumatologist according to special questionnaire form prepared for this purpose which includes (name, age, sex, residence, and family history, duration of rheumatoid arthritis, other diseases and medical history). Each subject who met the inclusion criteria completed a questionnaire, which gathered information on their demographic background. Blood samples were obtained from each patient, serum AST, ALT, ALP, GGT levels were determined according to the test kits procedure. The test kits for AST, ALT, ALP measurements were supplied by BioMerieux(France), the test kit for GGT was supplied by Biolabo(France), Rheumatoid factor was estimated by latex agglutination, and the test kit was supplied

by Biokit (Spain). The standard statistical methods for the analysis of data in this study were used to determine the mean, standard deviation (SD), paired and unpaired t-test. The statistical results were considered significant at $P \leq 0.05$ ⁽¹⁶⁾.

(*) significant difference exists at level 0.05 degree of significance.

(**) significant difference exists at level 0.01 degree of significance.

(***) significant difference exists at level 0.001 degree of significance.

Results

Mean values of enzymes activity show significant increase in patients when compared to controls (Table 1). No significant difference was found when the patients are compared according to different age range after their classification into three groups (<40 years, 40-50 years, >50years), except AST showed significant increase ($p = <0.05$) at 40-50 age group (Table 2). Comparison of serum liver enzymes activities in patients according to gender did not show significant difference except for ALP which show significant difference in female ($p = 0.0001$) (Table 3). For the relation between enzymes activities and duration of RA taking 5 years as cut off values in patients, the results in table (4) show non-significant increase for all enzymes activity. There was no significant difference in enzymes activity of patients when compared according to residence, according to family history and according to rheumatoid factor (Table 5, 6, 7 respectively).

Table (1):- Differences between patients and control subjects.

Enzymes	patients N=40		controls N=35		p-value
	Mean \pm SD	Range	Mean \pm SD	Range	
AST(IU/L)	27.6 \pm 15.5	9.0-95.0	22.3 \pm 6.7	10.0-31.0	0.05
ALT(IU/L)	28.4 \pm 13.2	8.0-73.0	22.1 \pm 7.3	7.0-31.0	0.01
ALP(IU/L)	55.3 \pm 49.7	17.5-308	48.7 \pm 16.7	22.4-91.0	0.01
GGT(IU/L)	16.3 \pm 15.7	4.1-94.0	11.1 \pm 5.4	3.0-23.6	0.05

Table (2):- Mean values of enzymes activity in patients according to age.

Enzymes	Age			p-value
	<40 years (N=10)	40-50 years (N=9)	>50 years (N=20)	
AST(IU/L)	24.30±9.08	38.88±25.69*	24.38±9.90	<0.05
ALT(IU/L)	25.00±6.78	29.22±16.88	29.76±14.06	(NS)
ALP(IU/L)	72.24±64.40	46.00±19.18	51.17±32.41	(NS)
GGT(IU/L)	23.41±22.02	21.77±20.98	10.66±10.25	(NS)

Table (3):- Mean values of enzymes activity in patients according to gender.

Enzymes	Gender		p-value
	Male (N=4)	Female (N=26)	
AST(IU/L)	25.75± 14.68	27.83± 15.85	(NS)
ALT(IU/L)	23.75± 6.34	28.97± 13.72	(NS)
ALP(IU/L)	24.15±5.74	58.73±51.24	0.0001
GGT(IU/L)	18.77± 17.29	19.05±16.08	(NS)

Table (4):- Mean values of enzymes activity in patients according to duration RA.

Enzymes	Duration of RA		p-value
	<5years (N=21)	≥5years (N=19)	
AST(IU/L)	25.94±11.35	29.14±18.75	(NS)
ALT(IU/L)	27.80±12.77	29.15±14.00	(NS)
ALP(IU/L)	46.00±25.90	64.40±63.70	(NS)
GGT(IU/L)	14.09±13.45	18.39±17.70	(NS)

Table (5):- Mean values of enzymes activity in patients according to residence.

Enzymes	Residence		p-value
	Rural(N=13)	Urban(N=27)	
AST(IU/L)	26.07± 10.58	28.37± 17.61	(NS)
ALT(IU/L)	25.84± 15.71	29.70± 11.95	(NS)
ALP(IU/L)	67.48±57.07	49.42±29.19	(NS)
GGT(IU/L)	23.30± 27.62	13.00± 11.68	(NS)

Table (6):- Mean values of enzymes activity in patients according to family history.

Enzymes	Family history		p-value
	Positive (N=13)	Negative (N=27)	
AST(IU/L)	25.61± 9.38	28.59± 17.89	(NS)
ALT(IU/L)	26.07± 8.13	29.59± 15.07	(NS)
ALP(IU/L)	44.73±24.85	60.34±57.75	(NS)
GGT(IU/L)	16.06± 14.71	16.48± 15.60	(NS)

Table (7):- Mean values of enzymes activity in patients according to rheumatoid factor.

Enzymes	Rheumatoid factor		p-value
	Positive (N=35)	Negative (N=5)	
AST(IU/L)	26.94± 11.08	32.4 ± 31.88	(NS)
ALT(IU/L)	28.97± 13.53	24.80 ± 11.25	(NS)
ALP(IU/L)	57.68±52.57	38.36± 13.51	(NS)
GGT(IU/L)	18.74± 15.83	20.12± 19.69	(NS)

Discussion

The statistical analysis of aminotransferase showed that there was a significant increase in the activity of both AST($p=0.05$) and ALT ($p=0.01$) when compared with control. Serum AST and ALT are excellent markers of hepatocellular injury (not necessarily the death of cells) where the injury is the trigger of the release of the enzymes into the circulation⁽¹⁷⁾. The significant increase in transaminases in this study was in agreement with the study of Fernandes and colleagues⁽¹⁸⁾ who found that some patients had marginal elevations of aspartate aminotransferase, other study made by Nancy J Walker⁽¹⁴⁾ reported that there is mild elevation in levels of serum aminotransferases. However, these results are in disagreement with the results of a study conducted by Thompson P. W. *et al*⁽¹⁹⁾ who demonstrated that serum transaminases are almost invariably normal. The statistically significant results of elevated Serum aminotransferases levels (AST and ALT) suggest the involvement of the liver cells during the

disease process of RA. However, despite the significant increase in serum aminotransferase activities compared with the control, the levels are still within normal ranges. There was also significant increase in alkaline phosphatase (ALP) in patients with RA when compared to control($p=0.01$). The results were in agreement with other studies, Carlo Selmi and Colleagues⁽¹²⁾ in 2011 said that elevated ALP have been reported in 18 to 50% of patients with RA, also The term rheumatoid liver was coined by Kendall and colleagues in 1970 based on the finding that 26% of patients with RA had elevated levels of ALP⁽¹⁴⁾. In 1979, a similar trend was reported by Fernandes, who observed that 35 patients of 100 had elevated level of serum ALP⁽¹⁸⁾. The results of the present study demonstrated a significant increase in the mean level of serum gamma glutamyl transpeptidase (GGT)($p=0.05$) , this finding was in consistency with other study made by Christine Schlenker and colleagues⁽¹⁵⁾ who found that increases in ALP and GGT

levels are the predominant biochemical abnormality in RA. Also Fernandes and colleagues⁽¹⁸⁾ found that 19 patients had a raised GGT. Serum GGT is regarded as sensitive indicator of hepatic disease where this enzyme is present in intra and extra duct cells and in hepatocytes⁽²⁰⁾. In the present study, the elevation of serum GGT had been more clearly manifested and it is more specific for liver disease. This may suggest bile duct involvement as well as the hepatocytes in the disease process of RA. Serum GGT has become one of the most important diagnostic tests for hepatobiliary disorders⁽²¹⁾. The importance of this test is that, it is not affected by bone disease or active growth and it is more sensitive than serum ALP in diagnosis of obstructive liver disease⁽²²⁾. No correlation could be detected between raised serum levels of liver enzymes and the age or sex of the patient and duration of arthritis. This study was conducted by Fernandes and colleagues⁽¹⁸⁾ and was in harmony with the present study, there was no significant difference according to age, sex and duration of the disease except for ALP was significantly increase in female when compared to male and this may be due to nature of RA which characterized by bone destruction and the disease is more common in female than male⁽¹⁾ or because women are more affected by osteoporosis(a bone disease characterized by elevation of ALP level)⁽²³⁾. There was also significant increase in AST at the age group 40-50 years. This elevation was difficult to explain it may be due to higher body mass index in this group of patients and a direct relationship between weight and AST is existed⁽²²⁾. However, the mean serum enzymes levels still within normal range. The comparison of the liver function test results between the patients residing in Mosul city (urban) with patients from rural areas has been performed. No significant difference had been found between the two groups suggesting no effect of the locality in the present study. The patients had been

divided into two groups according to their family history. The first group includes patients with positive family history and the second group includes negative family history. Liver function tests results had revealed non-significant difference for all parameters.

The patient also had been divided into two groups according to their rheumatoid factor. The first group includes patients with positive rheumatoid factor and the second group includes negative rheumatoid factor. Liver function tests results had revealed non-significant difference for all parameters. In conclusion, no changes in liver function tests were observed in rheumatoid patients as indicated by the normal levels of serum AST, ALT, ALP and GGT. However, a subclinical alteration in hepatic function could be expected in these patients. So that, monitoring of liver functions are recommended to be performed using more specific and early markers of hepatic dysfunction.

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