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# HOMOCYSTEINE LEVEL STATUS IN PATIENTS WITH RHEUMATOID ARTHRITIS IN DUHOK: IN RELATION TO DISEASE. ACTIVITY SCORE

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## ABSTRACT

**Rheumatoid arthritis (RA) causes high rate of the mortality. Cardiovascular disease (CVD) is markedly elevated in RA partly due to accelerated atherosclerosis (AS) from chronic inflammation. Homocysteine' elevation (Hcys) strongly related to the AS and CVD's progression in RA. Current study aims to evaluates Hcys level status and its relation with disease activity (DA) and inflammation marker (CRP) in Duhok RA patients.**

**Sixty-four RA patients (case) were involved in this study with equal number of healthy individuals (control), means± SD of their age were 47.78 ± 14.08 and 46.98 ± 15 respectively. ratio of females to males was (8.1 and 7.0) in case and control respectively. Blood was analyzed and RA related laboratory and biochemical markers were investigated.**

**The results revealed that Means±SD of Hcys was higher in case comparing to control (17.30±8.52 and 7.2±3.4) respectively. RA patient with high DA score recorded higher percentage intra group of increased Hcys level (52%).**

**This study concludes that there is a strong association between Hcys level and RA activity, severity and inflammation process in RA Duhok patients. Hcys could play role as a predictor marker helping physicians for good monitoring and managing RA disease.**

***KEYWORDS:*** RA, Hcys, ACCP, CRP, DAS28-CRP.

## INTRODUCTION

The risk of cardiovascular (CVD) morbidity and mortality is raised in Rheumatoid arthritis **(**RA) in comparison with general population (Agca R. et al.,2017; Van den Hoek,et al., 2017).Conventional CVD risk factors involving (hyperlipidemia, hypertension, obesity, insulin resistance, smoking, physical inactivity and diabetes mellitus) are highly prevalent among patients with RA and contribute to the CVD risk (Crowson et al., 2018). The Inflammation has a key role in all stages of AS -from endothelial dysfunction to plaque rupture and thrombosis-; thus, it is considered as a very important link between CVD and RA. It also affects and aggravates some classical risk factors of CVD (Meissner et al., 2016).

Common inflammatory pathophysiological mechanisms were shared by rheumatoid synovitis and unstable atherosclerotic plaque (Kerola et al.,2021). Newly, the elevation of Hcys is considered a strong contributor and a new risk factor for CVD (Borman et al., 2014). Increased of CVD and total mortality, increased incidence of -stroke, dementia, Alzheimer's disease and bone fractures-, and chronic heart failure is of greater prevalence which were associated with increased Hcys level (Selhub, 2006).

The correlation between the Hcys levels and commonly used inflammatory markers as C-reactive protein (CRP) in RA patients is not clear. It has been shown that RA may be associated with increased Hcys levels which might in turn, be associated with CVD events (Perna et al., 2010). More studies revealed that Hcys levels were higher in RA disease for the case group compared to control group. (Choi et al., 2014; Jednacz and Rutkowska, 2012, and Slot O., 2013). In this study, we investigated and evaluated the relation between Hcys levels status and inflammatory markers among RA



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patients. In addition, we also examined the correlation between disease activity and Hcys levels status in RA patients.

## SUBJECTS AND METHODS

### Subjects

The present comparative study involved 128 participants. Sixty-four were healthy subjects who were conducted to this study as control group and the remaining was RA patients recruited into study as case group. Patients were diagnosed with RA according to the ACR/EULAR 2010 criteria (American college of rheumatology/European League Against Rheumatism) (Aletaha et al., (2010)) they were attended Duhok Center for Rheumatic Disease and Medical Rehabilitation (DCRDMR) for managing and following-up. All patients were treated with MTX as treatment with an average weekly dose of 3.71±0.73 mg/week it has been taken orally throughout 7.97±0.77 years.

### Methods

Blood was drawn from each participant and afterward each sample has been analyzed. MTX blood levels were determined by Elisa kit using Bio Teck reader and washer made by USA. Homocysteine and CRP were determined using automated machine Cobas 6000(c501 the chemistry module) based on principle of turbidometry method, the machine was belonged to ROCH Diagnostic, Germany manufactured by Hitachi. ACCP was determined using same machine (e601 the immune assay part) based on principle of chemiluminescent immune assay (CLIA). Hcys levels were classified into to two categories based on its status: the first one is normal when its concentration in the blood was ≤ 15.0 umol/l and the second one was increased if the concentration exceeded 15.0 umol/l.

### Statistical analysis

Statistical analysis was performed using the IBM SPSS Version 25. for the distribution of variables with number and percentage and evaluating P-value, the cross-tab Pearson Chi-square test was used, while for determining and comparing means; one sample T-test and independent T-test were done. The 95% confidence interval(95%CI) and Odds Ratio (OR) were used for determination of the association. Two-sided P-value of less than 0.05 was considered as significant statistically.

## RESULTS

### Distribution of disease-related general characteristic between RA patients and healthy individuals

The comparison between distributions of disease -related characteristics between RA patients and healthy individuals is shown in **Table 1**.

Results of this study did not find any significant difference between both group regarding demographic characteristic while significant difference of clinical and biochemical characteristic is observed between RA patients and healthy individuals $p< 0.05$. However, mean ± SD of ACCP, Hcys and CRP in RA patients were markedly greater when compared to their value in healthy individuals. Mean of age of RA patients was 47.78±14.08 and healthy subjects was 46.98±15.1which were very close each other. Females to males ratio of RA patients was 8.1

**Table( 1):- General characteristics of the participants between RA patients and healthy subjects.**

| Characteristics | RA patients Mean±SD | Healthy subjects Mean±SD | P-value |
|---|---|---|---|
| **1-Demographic** | | | |
| Age (years) | 47.78±14.08 | 46.98±15.1 | 0.67 |
| Male N (%) | 7(10.9) | 8(12.5) | 0.78 |
| Female N (%) | 57(89.1) | 56(87.5) | |
| F/M ratio | 8.1 | 7.0 | |
| **2-Clinical** | | | |
| DAS28-CRP (score) | 4.38±1.42 | / | |
| RA duration (years) | 11.19±7.55 | / | |
| **3-Biochemical** | | | |
| ACCP (U/ml). | 106.46±95.64 | 5.2±2.3 | 0.00 |
| CRP (mg/l.) | 25.06±20.06 | 3.9±1.7 | 0.00 |
| Hcys levels (umol/l) | 17.30±8.52 | 7.2±3.4 | 0.00 |

**Distribution of RA duration and swollen and tender Joints between Hcys levels group.**

The distribution of RA duration and swollen Joints as well as tender Joints between Hcys levels groups has been demonstrated in **Table 2.**

No significant difference was found between Hcys levels status groups and RA duration as well as swollen joints groups among RA patients (P>0.05) while concerning tender joints group, the deference was significant between both Hcys groups p<0.05.

However, RA patients with duration disease of longer than five years had higher number and percentage of distribution in increased homocysteine levels group 29(72.5%) comparing to those with 5 years or less 11(27.5%). Number of swollen joints exceeded six were significantly associate with increased Hcys levels (OR: 5.0, p<0.05). tender joints of 1 to ≤6 and >6 was significantly associated with Hcys high levels (OR: 30 and 25, p<0.05). In addition, number of RA patients with swollen or tender joint had increase Hcys level than those who had none of them, SWJ; 32(80%) vs 8(20%) and TNJ; 39(97.5%) vs 1(2.5%).

**Table (2):-** Distribution of RA patients concerning duration, swollen joints and tender Joints based om Hcys levels.

| Disease -Related Clinical Characteristics | Hcys Increased level >15 umol/l N(%) | Hcys Normal level ≤ 15 umol/l N(%) | OR, 95% CI | P-value |
|---|---|---|---|---|
| **RA duration** | | | | 0.826 |
| ≤ 5 y | 11(27.5) | 6(25.0) | 1.14[0.36-3.61] | / |
| >5 y | 29(72.5) | 18(75.0) | 0.88[0.28-2.79] | / |
| **Swollen Joint** | | | | 0.77 |
| non-swollen joint | 8(20.0) | 10(41.7) | / | / |
| Join | 16(40.0) | 10(41.7) | 2.0[0.59-6.77] | 0.263 |
| >6 joint | 16(40.0) | 4(16.7) | 5.0, [1.19-21.04] | 0.023 |
| **Tender Joint** | | | | 0.000 |
| Non-tender joint | 1(2.5) | 10(41.7) | / | / |
| 1-6 Joint | 15(37.5) | 6(25.0) | 25[2.6-240] | 0.001 |
| >6 joint | 24(60.0) | 8(33.3) | 30.0, [3.3-272] | 0.000 |

**Table (3):** Distribution of RA patients regarding disease activity based on Hcys levels.

| Disease -Related Clinical Characteristics | Hcys Increased level >15 umol/l N(%) | Hcys Normal level ≤ 15 umol/l N(%) | OR, 95% CI | P-value |
|---|---|---|---|---|
| **DAS28-CRP** | | | | 0.000 |
| Remission ≤ 2.6 | 2(5.0) | 12(50.0) | / | / |
| Low 2.6< and ≤ 3.2 | 0(0.0) | 1(4.2) | 0.6[0.00-473] | 0.879 |
| Moderate 3.2< and ≤5.1 | 17(42.5) | 7(29.2) | 14.57[2.57-82.73] | 0.001 |
| High >5.1 | 21(52.5) | 4(16.7)) | 31.0 [5.0-198.2] | 0.000 |

Distribution of RA patients regarding disease activity based on Hcys levels.

Distribution of RA activity between Hcys levels groups is shown in **Table 3**, Significant difference between Hcys levels groups regarding DAS28-CRP was observed p<0.05.

As RA to be more active as Hcys will increase. RA patients with high and moderate DAS28-CRP score recorded larger number and distribution percentage in increased Hcys level group than in low and remission 38(95%) vs 2(5%). In addition, the majority of RA patient with high and moderate DAS28-CRP has elevation Hcys level >15 umol/l, 21(84%) and 17(70.8%) respectively. The aggravation of disease through moderate toward high DAS was significantly associated with increases of Hcys concentration exceeding upper normal range (OR: 14.57 and 31.0, p<0.05), **Figure 1**.

**Distribution of RA patients regarding disease severity based on Hcys levels.**

Distribution of RA severity between Hcys levels groups is shown in **Table 4**, Significant



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difference between Hcys levels groups regarding RA severity was observed p<0.05.

Beginning from low severity through moderate to high severity, number and distribution percentage were observed in increasing manner in group of elevation Hcys concentration over (15 umol/l). The minority of RA patient with high severity had larger number of elevated Hcys level. RA severity was significantly associated with raised Hcys levels. (OR: 14.0 and 10.5, p<0.05) with moderate and high severity respectively.

**Table (4): -** Distribution of RA patients regarding disease severity based on Hcys levels.

| Disease -Related Clinical Characteristics | Hcys Increased level >15 umol/l N(%) | Hcys Normal level ≤ 15 umol/l N(%) | OR, 95% CI | P-value |
|---|---|---|---|---|
| **RA severity** | | | | 0.000 |
| Low | 5(12.5) | 15(62.5) | / | / |
| Moderate | 14(35.0) | 3(12.5) | 14.0[2.81-69.76] | 0.001 |
| High | 21(52.5) | 6(25.0) | 10.50[2.70-40.88] | 0.000 |

**Comparison of Mean± SD of disease -related biochemical characteristics among RA patients with different Hcys level status groups.**

Comparison of Mean± SD of inflammation marker and immunological antibody among RA patients with different Hcys level status groups are illustrated in **Table 5.**

Mean of increased Hcys levels was significantly two-fold higher than mean of Hcys normal levels 21.44±8.18 and 10.38±2.32 respectively. RA patient who their Hcys level increased have also significantly greater Mean± SD of CRP 30.66±18.26 and ACCP 138.40±91.12 than those with normal level of Hcys significantly p<0.05.

**Table( 5):-** Comparison of Mean± SD of disease -related biochemical characteristics among RA patients with different Hcys level status groups.

| Biochemical characteristics | HCYS increased level >15 Mean± SD | HCYS normal level ≤ 15 Mean± SD | P-value |
|---|---|---|---|
| **Hcys Level (**umol/l) | 21.44±8.18 | 10.38±2.32 | 0.000 |
| **CRP (**mg/l.)) | 30.66±18.26 | 15.74±19.79 | 0.000 |
| **ACCP** (U/ml) | 138.40±91.12 | 53.23±79.04 | 0.000 |

**Distribution of disease-related biochemical characteristics among RA patients with different Hcys levels status groups.**

Among RA patients with different Hcys level status groups, disease -related biochemical characteristics were distributed. This is demonstrated in **Table 6.**

Significant deference was observed between number and distribution percentage of ACCP and CRP levels group<0.05. The maximum distribution percentage of positive CRP was belonged to RA patients with high Hcys level 38(80.85%), **Figure 2**. Same observation was revealed in respect to positive ACCP 37(78.72%). Additionally, strong association was seen between the elevation of CRP level and ACCP level, and raised Hcys level (OR:31.67and 20.56, p<0.05).

**Table (6):-** Distribution of disease -related biochemical characteristics RA patients with different Hcys level status groups.

| Biochemical characteristics | HCYS Increased level >15 N(%) | HCYS (N=24) Normal level < 15 N(%) | OR, 95% CI | P-value |
|---|---|---|---|---|
| **Hcys Level** | 40(62.5) | 24(37.5) | / | 0.000 |
| **CRP** | | | | |
| Normal | 2(5.0) | 15(62.5) | 0.03[0.01-0.16] | 0.003 |
| Positive | 38(95.0) | 9(37.5) | 31.67[6.11-164.01] | / |
| **ACCP** | | | | |
| Normal | 3(7.5) | 15(62.5) | 0.05[0.01-0.2] | 0.000 |
| Positive | 37(92.5) | 9(37.5) | 20.56[4.88-86.57] | / |

Correlation between disease-related characteristics among RA patients

The correlation between disease-related clinical characteristics among RA patients is demonstrated in **Table 7.** Hcys levels was strongly and significantly correlated with DAS28-CRP, CRP and ACCP

**Table (7):-** Correlations between RA related variables

| | | DAS-28 | ACCP IU/ml | CRPL mg/L | HCYST umol/l | MTX ng/ml |
|---|---|---|---|---|---|---|
| **DAS-28** | Pearson Correlation | 1 | 0.681** | 0.691** | 0.424** | .510** |
| | Sig. (2-tailed) | | 0.000 | 0.000 | 0.000 | 0.000 |
| **ACCP IU/ml** | Pearson Correlation | 0.681** | 1 | 0.700** | 0.511** | 0.435** |
| | Sig. (2-tailed) | 0.000 | | 0.000 | 0.000 | 0.000 |
| **CRPLX mg/L** | Pearson Correlation | 0.691** | 0.700** | 1 | 0.366** | 0.405** |
| | Sig. (2-tailed) | 0.000 | 0.000 | | 0.003 | 0.001 |
| **HCYST umol/l** | Pearson Correlation | 0.424** | 0.511** | 0.366** | 1 | 0.306* |
| | Sig. (2-tailed) | 0.000 | 0.000 | 0.003 | | 0.014 |

**. Correlation is significant at the 0.01 level (2-tailed)

*. Correlation is significant at the 0.05 level (2-tailed).

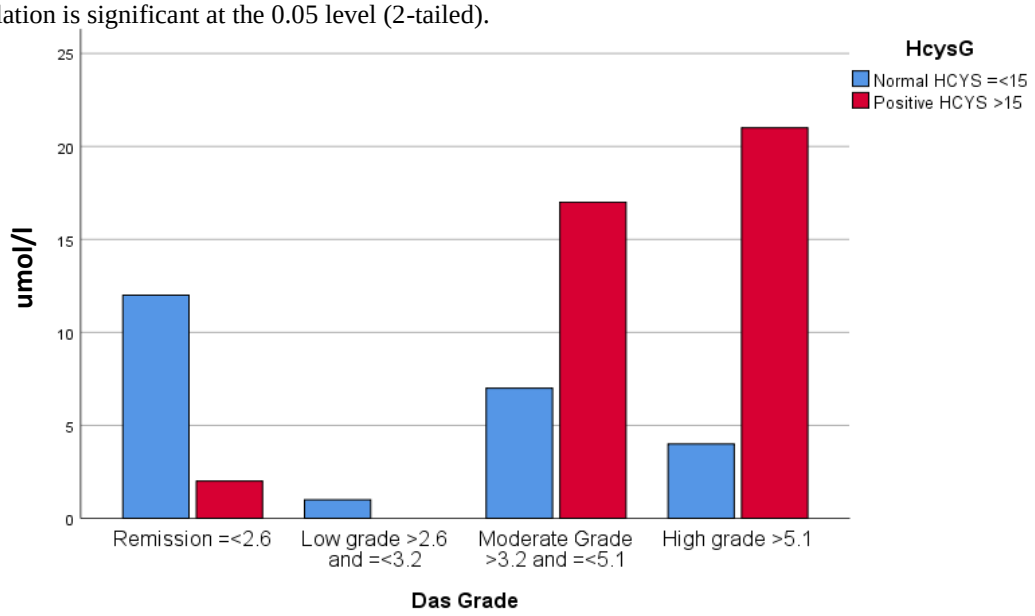


**Fig.( 1)**: -Distribution of Hcys levels Status among DAS28-CRP grade of RA patients' groups

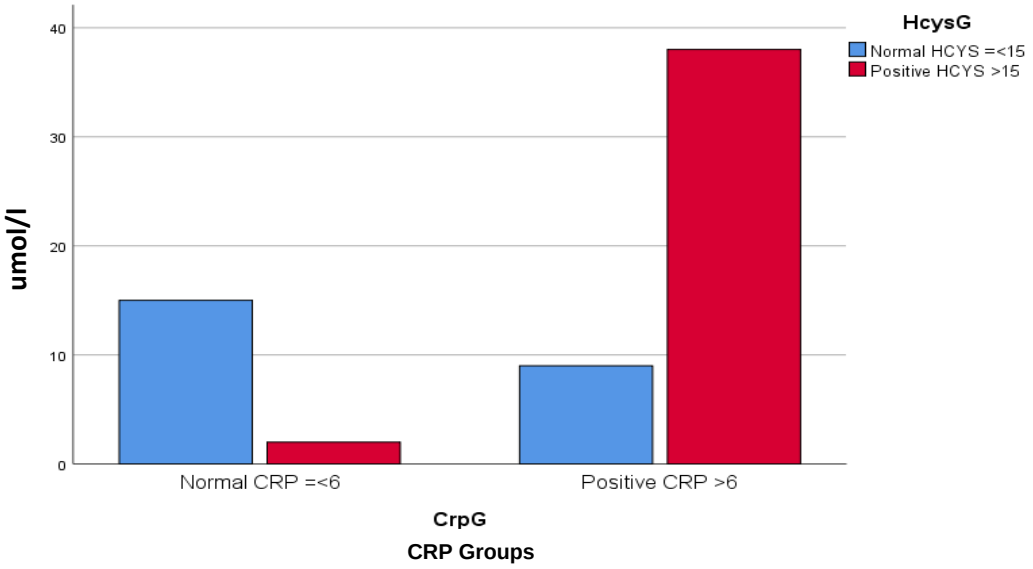


**Fig.( 2)**: -Distribution of Hcys levels Status among CRP levels groups of RA patients

## DISCUSSION

Our study investigated the relation between Hcys level and RA activity score among Duhok patients with RA attending Duhok center for Rheumatology and Medical Rehabilitations (DCRMR), Duhok, Iraq. The results were revealed that patients with RA have elevated Hcys level to extent exceeded upper normal range value and was higher than in healthy individuals. Similarly, same findings were detected by other studies (Vasiljevic et al,.2015, and Abd El-Aziz TA and Mohamed RH. 2017).

Current study also analyzed the relationship of inflammation marker and/or immunological marker in RA patient with Hcys levels, because, currently, it has been sighted that the systemic inflammation speeds up atherogenesis and metabolic and immunologic marker as Hcys and ACCP; could have role in the atherosclerotic disease progression in RA patients (Rezuș et al..2015), this supposition is supported by the large rate of cardiovascular mortality and morbidity and the prevalence in large portion of all stages of atherosclerosis and complications among patients with RA (Agca et al.,2017). Also, a conventional and non-conventional risk factors of CVD's following-up and universal assessment, in addition to true sorting of categories of risk reduction, are interesting for the RA study. ( Reiss et al., 2019, Szekanecz et al., 2007).

Our results detected that, the inflammation marker as CRP was passed the upper reference value to attained higher level in RA patient comparing with healthy subjects. Recurrent elevation of CRP might have linkage to accelerating atherosclerosis. Constantly raising CRP level through RA course might cause increase risk of CVD and subsequently risk of death increases as well (Janet et. al., 2021, Badimon, et al., 2018).

In addition, we also observed the significant correlation of CRP with Hcy levels and association of positive CRP with increased Hcys level in RA patients. So, the elevation of Hcys level together with CRP as inflammatory marker parallel leading to revealed that Hcys could influence the status of inflammatory and might be a predictor sign of increased Hcys level in RA patients.

Furthermore, Liu et al., revealed that Hcys has a significant association with the subclinical atherosclerotic process and it showed potential as a cheap marker for risk dividing among asymptomatic patients (Liu et al., 2018). This pushing us to propose that inserting Hcys test in the protocol of futuer risk reduction for indicating high risk of atherosclerotic events of RA patients in order to classify them for more aggressive therapy with established preventive and therapeutic measures. (Liu et al., 2018; Selhub, 2006).

Regarding RA disease activity, our study observed that Hcys was correlated with the RA disease activity and increased Hcys level was significantly associated with high grade of DAS28-CRP. Some studies revealed that activity of RA disease was strong forecast of Hcys levels (Nowakowska-Plaza et al., 2014). While Van Ede AE et al.,(2020) observed that no association between amelioration of disease activity and increased Hcys level.

Moreover, Galiutina and Bychak were showed that RA patient with increased Hcys level and active inflammation process (painful, number of swollen joints, DAS28, CRP) had association by myocardial ischemia. So, for reaching good control and overcoming inflammation and immunologic and metabolic disorders, it is very important to diagnosis and evaluate CVD risk factor following by aggressive prevention and therapy. Thus, Hcys could play a strong role as a marker of atherosclerotic disease than having role as risk factor for atherosclerotic disease. In addition, identifying patients with risk factors in time, helps to get good prevention of and therapy for CVD in RA patients.

In conclusion, our study revealed that, there is a strong association of Hcys level with RA activity, severity and inflammation process in RA Kurdish patients. Hcys could play role as a predictor marker helping physicians for good monitoring and managing RA disease and delaying and/or preventing them from RA associated complications as CVD.

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