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Measurement of the Common Carotid Arteries Intima-Media Thickness by Ultrasonography in Patients with Rheumatoid Arthritis

Romatoid Artritli Hastalarda Ortak Carotid Arteri Intima-Media Kalınlığının Ultrasonografi ile Ölçümü

Raouf Rahim Merza[1], Salah Muhammed Fateh[1], Hawar Ali Ehsan[1]

[1]Sulaimaniya Medical School, Rheumatology Iraq,

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ABSTRACT

Purpose: Rheumatoid arthritis is a chronic inflammatory disabling disease affecting articular and extra articular organs and one of these important organs is cardiovascular system, whose involvement is a leading cause of morbidity and mortality of Rheumatoid arthritis patients. Therefore, it is important to look for the relation of Rheumatoid arthritis and the extent of cardiovascular involvement among those patients by Ultrasound (US) which is feasible, simple and low cost investigation. Moreover, sonographic measurement of carotid artery intimal thickness is one of those reliable and sensitive means in assessing generalized atherosclerosis. To determine whether arterial wall thickening is increased in Rheumatoid arthritis patients compared with healthy controls by measuring the intima-media thickness of the common carotid arteries and to evaluate the factors that may be responsible for arterial intima-media thickness increase in patients with Rheumatoid arthritis.

Material and Methods: 32 Rheumatoid arthritis patients (7 males and 25 females) been evaluated for common carotid intima-media thickness compared with 30 healthy control subjects (8 males and 22 females) matched for (age, sex, and other major risk factors for atherosclerosis). Laboratory variables were measured by routine methods. Intima-media thicknesses of the common carotid arteries were measured by High-frequency linear probe ultrasound.

Results: Common carotid artery intima-media thickness was significantly higher (P-value 0.003) in Rheumatoid arthritis patients (mean±SD 0.66±0.11mm) compared with controls (0.58±0.086mm).There was a highly significant association between carotid intima-media thickness increase and the acute phase reactants (ESR, CRP) and Rheumatoid factor as P-value was (0.000, 0.001 and 0.000) successively. No relation between carotid intima-media thickness and duration of disease modifying anti-rheumatic drugs usage was found (P-value 0.051).

Conclusion: Rheumatoid arthritis patients are around three fold at a higher risk of developing arterial intimal thickening and in turn they are more prone to develop cardiovascular complications than normal population due to the effects of chronic inflammatory processes and these results concluded that the disease modifying anti-rheumatic drugs has no protective measures on arterial intima-media wall thickening.

Key Words: Rheumatoid arthritis, Carotid intima-media thickness, Ultrasonographic measurement.

ÖZET

Amaç: Romatoid Artrit; eklemsel ve eklem harici organları etkileyen kronik inflamatuvar hastalıktır. Bu hastalığın etkilediği önemli organ sistemlerinde bir tanesi de Romatoid Artrit'li hastalarda mortalite ve morbidite oranlarının yükselmesine yol açan kardiyovasküler sistemdir. Dolayısıyla, Romatoid Artrit'li hastalar arasında hastalığın görülme oranını araştırmakda fayda sağlayacağı gibi uygulanabilir, basti ve düşük masraflı ultrasongrafi aracılığıyla

kardiyovasküler sistemin ne derece katılım gösterdiğini bulmak değerli bir araçtır. Ayrıca karotid arter intimal kalınlığı ölçümü aterosklerosis değerlendirilmesinde de uygulanabilecek hassas yöntemlerden bir tanesidir. Çalışmamızın amacı Karotid arterlerinin intimal-media kalınlığını ölçerek sağlıklı kontroller ile karşılaştırarak Romatoid Artriti bulunun hastalarda arteriyal duvar kalınlığında artış olup olmadığını belirlenmek ve böylece Romatoid Artrit hastalarında artan arteriyal intima-medya kalınlığına neden olabilen faktörleri değerlendirmektir.

Materyal ve Metod: 32 Romatoid Artrit hastası (7 erkek ve 25 kadın), 30 sağlıklı kontrol (yaş, cinsiyet ve atheroskleroz riskleri açısından uyumlu) karotid intima-media kalınlığı açısından karşılaştırılıp değerlendirildi. Laboratuvar değerlendirmeleri rutin yöntemler ile ölçüldü. Karotid arterlerin intima-media kalınlığı yüksek frekanslı lineer ultrasound probu ile ölçüldü.

Bulgular: Karotid arter intima-medya kalınlığının kontrollere kıyasla Romatoid Artrit hastalarında önemli derece de artış gösterdiği belirlenmiştir (p-değeri: 0.003). Karotid intima-media kalınlığı artışı, akut faz reaktantları (ESR, CRP) ve romatoid faktörleri arasında önemli derecede ilişki bulunmuştur ve P değeri sırasıyla 0.000, 0.001 ve 0.000 olarak tespit edilmiştir. Karotid intima-media kalınlığı ile hastalığı düzenleyen anti-romatizmal ilaç kullanımı süresi arasında herhangi bir ilişki bulunmamıştır (p- değeri: 0.051)

Sonuç: Romatoid Artrit hastalarında arteriyal intimal kalınlığı artışı control grubuna gore üç kat daha fazladır. Dolayısıyla bu tip hastalarda kardiyovasküler komplifikasyonların görülme olasılığı kronik inflamatuvar süreçlerinin etkilerinden dolayı normal populasyonlara göre çok daha fazladır. Hastalığı düzenleyen anti-romatizmal ilaçların arteriyel intimal-medial duvar kalınlaşması üzerine herhangi bir koruyucu etkisi olmadığı sonucuna varıldı.

Anahtar Kelimeler: romatoid artrit, karotid intima-media kalınlığı, ultrasonografik ölçüm

INTRODUCTİON

Rheumatoid arthritis is a chronic autoimmune inflammatory disease affecting joints and several organs, like lungs, serosa, heart, and the peripheral nervous system[1].It characterized by chronic and erosive polyarthritis caused by abnormal growth of synovial tissue or pannus, and causes irreversible joint disability. It is the most common inflammatory arthritis, affecting from 0.5 to 1% of the general population worldwide with a female/male ratio of 2.5:1. The disease may appear at any age, but it is most common among those aged from 40 to 70 years and its incidence increases with age. Apart from pain, RA is associated with reduction of functional capacity, and increased comorbidity and mortality[2]. With prevalence in Iraq is around 1 %[3].

The disease is of unknown etiology but several factors are clearly implicated in its etiology and pathogenesis, i.e. genetic factor, hormonal, autoimmunity, environmental factors (e.g. smocking)[4].

It is well recognized that rheumatoid arthritis (RA) causes significant morbidity as a result of synovial inflammation, joint destruction, and associated disability. In addition to these articular manifestations of RA, there is growing recognition of an excess mortality, which is predominantly due to increased coronary artery atherosclerosis. Approximately 50% of atherosclerotic coronary artery disease in the community occurs in the absence of traditional risk factors, such as smoking, hypertension, diabetes mellitus, and hypercholesterolemia[5].

Histological studies have demonstrated the importance of inflammatory mediators (including activated leukocytes, cytokines, and C-reactive protein [CRP]) within atherosclerotic plaque; further, in large, prospective, epidemiologic studies, elevated serum levels of markers of inflammation (e.g., CRP and serum amyloid A [SAA]) were predictive of future cardiovascular events. Chronic inflammation may act independently or synergistically with traditional atherosclerotic risk factors in the pathogenesis of atherosclerosis and may also be associated with a hypercoagulable state. RA and other chronic systemic inflammatory diseases may provide insight into these interactions[5-8].

There is increasing interest in the role of inflammatory and immunologic mechanisms in the initiation and progression of atherosclerosis. This reassessment is based on a number of

observations, including the abundance of monocytes, macrophages, and T lymphocytes in atherosclerotic plaques. CRP, SAA, and activated complement components are also present in plaque tissue[8,9]. In animal models of atherosclerosis induced by a high-cholesterol diet, the earliest cells to adhere to the endothelium are monocytes, which migrate to subendothelial layers, engulf oxidized cholesterol, and differentiate into macrophages. Activated macrophages and T lymphocytes release or induce a variety of inflammatory mediators, including cytokines (e.g., interleukin-1 [IL-1], tumor necrosis factor [TNF]), growth factors, adhesion molecules, and matrix metalloproteinase. This results in further recruitment of inflammatory cells, migration and proliferation of endothelial and smooth muscle cells, collagen breakdown, platelet aggregation, in situ thrombosis, loss of endothelial nitric oxide, and release of oxygen free radicals. These processes contribute to the formation of atherosclerotic plaque and share many features with the pathology of RA[5].

Proinflammatory cytokines (TNF-a, IL1-b, and IL-6) play both a direct role and an indirect role in the genesis of atherosclerosis in patients with inflammatory diseases. In patients with RA, proinflammatory cytokines produced by the rheumatoid synovium may diffuse within the bloodstream where they may alter the function of numerous tissues including fat, skeletal muscle, liver, and vascular endothelium. These functional alterations may induce changes that promote atherogenesis, such as insulin resistance, increased oxidative stress, endothelial dysfunction, and dyslipidemia[9].

Persistent endothelial dysfunction predisposes to organic damage of the vascular wall that, in a preclinical stage, before overt disease, can be detectable by ultrasound measurement of carotid intima-medial thickness (CIMT). Many investigations showed evidence of increased carotid IMT in RA[10-12]. Ultrasonographic assessment of common carotid atherosclerosis is a feasible, reliable, valid, cost-effective and noninvasive method for both population studies and clinical trials of atherosclerosis progression and regression[13-16]. The common carotid artery IMT is strongly correlated with the presence of coronary artery diseases[16-19] and the association between CIMT and CV disease has been well established[20-23]. Carotid intima-media thickness was shown to have an extremely positive predictive value for identifying individuals with angiographically defined coronary artery disease[24].

MATERIAL and METHODS

Patients and controls: Subjects of the present study were 32 RA patients (7 males and 25 females) aged between (40-69yr.) and 30 healthy control subjects (8 males and 22 females). The RA patients were selected from the patients attending the Outpatient Clinic of Rheumatology And Rehabilitation at Sulaimaniya City and from the patients admitted to the General Hospital /department of Rheumatology between January and August 2010,whom have already established R.A and were diagnosed according to the 1987 revised criteria of the American College of Rheumatology[25].

The 30 healthy control subjects were selected from among paramedical personnel whom are working in the General and teaching Hospital of Sulaimaniya after obtaining their consent.

To avoid confounding by other known risk factors for atherosclerosis, patients with hypertension, hyperlipidemia, diabetic mellitus (DM), peripheral vascular diseases, hypothyroidism and renal diseases). Or having history of ischemic heart disease or cerebrovascular events been excluded from the study. All patients were receiving one or combinations of Disease Modifying Anti-Rheumatic Drugs [DMARDs], Patients were on irregular NSAIDs ingestion & none of the patients was receiving regular glucocorticoids or any kind of

biological agents. Both groups (patients & controls) were comparable in age and sex and were not smokers, alcoholic, or obese.

Laboratory tests: Tests for acute phase reactants (ESR &CRP) Rheumatoid Serum Factor) [RF], fasting blood sugar & lipid profile been done for all patients and control subjects. R.F. was estimated by ELISA.

Ultrasonographic determination of the Intima-Media Thickness [IMT] of the common carotid arteries: The patient was placed in the supine position for ultrasonographic examination of the common carotid artery by High-frequency linear probe ultrasound (model Fukuda-Danshi Co. LTD Japan UF-870AG). All measurements were done by single operator and made manually on digitized still images that were obtained during ultrasound scanning and the radiologist was unaware of the clinical characteristics of the subjects. The common carotid artery was scanned on both right and left sides & average was taken as used figures. The IMT was measured by obtaining the lowest value of intimal thickness to avoid any present atheromatous plaque (localized lesions more or equal to 2.0 mm in thickness) in the arterial wall[26,27].

Statistical Analysis: Different statistical analyses were carried out using statistical package for social science (SPSS) version 16.0 windows.

Statistical analysis included both descriptive and inferential statistic for analyzing the data obtained from the study to explain the results, Chi square for categorical data, ANOVA and T test used for continuous data to determine the level of significance (P-value). A P = 0.05 and less was considered statistically significant.

RESULTS

Table No. (1): Age and Gender frequency distribution.

Parameter	Controls		(RA)Patients	
	N	%	N	%
Age				
40-49	13	43.3	9	28.1
50-59	12	40.0	16	50.0
60-69	5	16.7	7	21.9
Total	30	100.0	32	100.0
Gender				
Male	8	26.7	7	21.9
Female	22	73.3	25	78.1
Total	30	100.0	32	100.0

This table shows that the vast majority of the subjects (patients and healthy) (28 out of 62) were among the (50-59) age group, and that females are predominant (47 out of 62).

Table No. (2): Acute Phase Reactants and R.F. Status.

Parameter	Controls	(RA)Patients
	N (%)	N (%)
ESR		
Normal	30(100)	18(56.25)
Increased	0(0.0)	14(43.75)
Total	30(100)	32(100)
CRP		
Negative	30(100.0)	14(43.75)
Positive	0(0.0)	18(56.25)
Total	30(100)	32(100)
Rheumatoid factor		
Sero positive	0(0.0)	20(62.5)
Sero negative	30(100.0)	12(37.5)
Total	30(100)	32(100)

This table shows that the percentages of abnormal ESR, positive CRP and positive R.F. was (43.75%, 56.25% and 62.5%) successively.

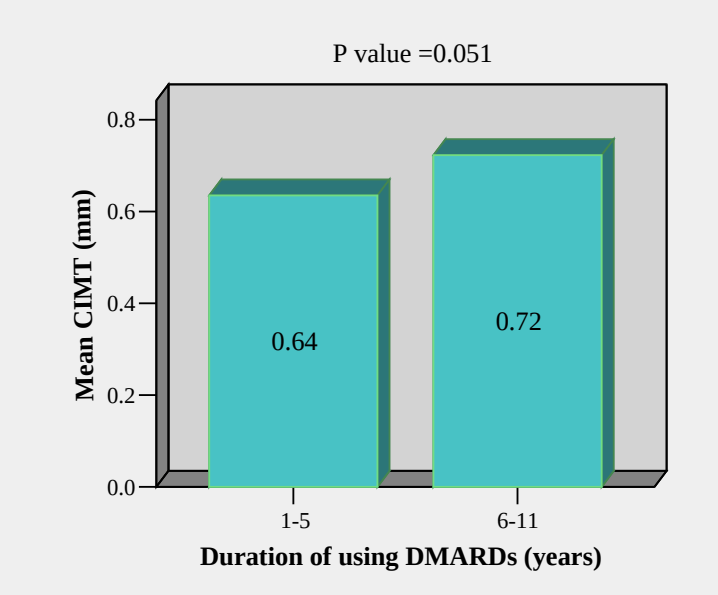

Figure 1. Association between DMARDs usage duration and CIMT.

This Figure shows no significant relation between CIMT and DMARDs usage (P-value 0.051).

Table No. (4): Association between common carotid artery IMT and Age and Gender in RA patients and controls.

Parameter	CIMT (mm) Among non-rheumatoid (controls) Mean ± Std. Deviation	P value	CIMT (mm) Among rheumatoid patients Mean ± Std. Deviation	P value
Age 40-49 50-59 60-69	 0.55 ± 0.054 0.57 ± 0.058 0.70 ± 0.12	 0.001	 0.57 ± 0.11 0.69 ± 0.94 0.73 ± 0.11	 0.008
Gender Male Female	 0.59 ± 0.10 0.58 ± 0.07	 0.445	 0.70 ± 0.13 0.66 ± 0.11	 0.445

This table shows that there is a significant relation between the age and the CIMT in patients P-value (0.008) but there was no relation between the gender and the CIMT P-value (0.445), furthermore shows that there is a significant relation between the age and the CIMT in healthy subjects P-value (0.001) while there was no relation between the gender and the CIMT (P-value 0.445).

Table No. (5): Association between common carotid artery IMT and Acute phase reactants and Rheumatoid Factor.

Parameter	CIMT (mm) Among rheumatoid patients Mean ± Std. Deviation	P value
ESR Normal Abnormal (increased)	 0.60 ± 0.091 0.75 ± 0.097	 0.000
CRP Positive Negative	 0.72 ± 0.08 0.59 ± 0.11	 0.001
Rheumatoid factor Sero positive Sero negative	 0.72 ± 0.10 0.57 ± 0.08	 0.000

This table is showing the highly significant association between the CIMT increase and the ESR, CRP and R.F. as P-value was (0.000, 0.001and 0.000) successively.

Table No. (6): Common Carotid Artery IMT among Patients and Controls.

Parameter	Controls	Patients	P value
	N (%)	N (%)	
Increased CIMT	6(20)	22(68.75)	0.003
Normal CIMT	24(80)	10(31.25)	
CIMT Mean ± Std. Deviation(mm)	0.58±0.086	0.66±0.11	

This table shows that The CIMT was significantly higher in RA patients (0.66 ± 0.11 mm) than in control subjects (0.58 ± 0.086 mm) (p-value 0.003). 68.75% of the RA patients were with increased CIMT.

DISCUSSION

Rheumatoid arthritis is a chronic inflammatory disabling disease affecting articular and extra articular organs [(1)] and one of those important organs is cardiovascular system which its involvement is blamed to be the number one responsible for the increased morbidity and mortality of RA patients [(28-36);] therefore it is important to look for the relation of RA disease and the extent of cardiovascular involvement among those patients by a feasible, simple and low cost investigation and one of those investigations is ultrasonographic measurement of carotid artery intimal thickness which was proved to be reliable and sensitive in assessing generalized atherosclerosis[13-16,37-41].Despite that both patients and healthy subjects were comparable in age, sex and risk factors of cardiovascular diseases, Our results showed that the carotid intima-media thickness (CIMT) was significantly higher in RA patients (0.66±0.11mm) than in control subject (0.58±0.086 mm) (p-value 0.003) which is statistically significant, nearly a similar results was concluded by Yasuro Kumeda et al[(42)] whom found IMT of the common carotid artery of (0.641 ± 0.127 mm) in patients which was higher than the control subjects (0.576 ± 0.115 mm) (*P-value* 0.0001).

As increased carotid intima–media thickness (IMT) and carotid plaques have been proved to predict the development of CV events in RA, the authors suggest performing carotid ultrasound when the systematic coronary risk evaluation (SCORE) does not yield results indicating high CV risk in RA patients which are extra-articular manifestations, RF or anti-CCP positivity as well as in patients with 10 years disease duration or longer[43].

In the present study we found that there is association between (CIMT) and acute phase reactants, i.e., patients with Positive CRP have (IMT) of (0.72 ± 0.08mm) which was greater than those with negative CRP (0.59 ± 0.11mm) (p-value 0.001) which is significant ; and patients with high ESR have (IMT) of (0.75 ± 0.097mm) which was greater than those with normal ESR (0.60 ± 0.091mm) (p-value 0.000) which is highly significant, these results are comparable with the results carried out by Inmaculada del Rinco´n et al[(10)] whom found that the increase of (CIMT) significantly associated with the inflammatory markers in the form of CRP (p-value 0.005) and ESR (p-value 0.008) after age, sex and CV adjustment. As it is clear that the association between the (CIMT) and CRP in del Rinco´n et al[10] study is greater than that with ESR which is the opposite in ours which could be explained by that we used the conventional method to check CRP; moreover some studies showed no significant association between increased (CIMT) and abnormal ESR[42,44]; based on previous results the inflammatory markers can be the cause behind this increase in (CIMT) among RA patients[5-8,45]. Furthermore we found that patients with sero-positive (RF) have higher (CIMT) (0.72 ± 0.10mm) than those with sero-negative (CIMT) (0.57 ± 0.08mm) (p-value 0.000) which is strongly significant. This is consistent with the statement that assigns a role of sero-positivity of RA in the complications of this disease which is one of the bad prognostic signs of RA disease[46,47.] Regarding the (CIMT) and the age we found that there is a significant relation between the age and the CIMT in both the patients and the healthy subjects P-value (0.008, 0.001) successively, but the CIMT increase among the patients is greater than those among healthy and this is due to their disease course and chronic inflammatory processes; While

the relation between the gender and the CIMT in both groups did not reach a statistical significant level (P-value 0.445), but the intimal thickness increase in RA males was greater than RA females (0.70 ± 0.13mm) (0.66 ± 0.11mm) respectively and this might indicate more severe vascular involvement in RA males than in RA females.

There are several possible explanations for the observed association between arterial wall thickness and RA. The first is a possible relationship between atherosclerosis and chronic inflammation due to RA. It has recently been hypothesized that inflammation plays a major role in the process of atherosclerosis[5-9,48].CRP has been hypothesized to play a major role in this (CIMT) increase as it involves pathophysiology of atherosclerosis and its complications[49,50,51] and this what we and Inmaculada del Rinco´n et al[10] found in our studies. The second possibility is that the arterial wall changes is due to RA associated bone destruction as many studies showed evidence that atherosclerosis progresses significantly faster in patients with enhanced bone destruction than in those with less bone destruction[52,53,54]. The third possibility is that the atherosclerosis is more in patients with low physical activity due to their disease nature of disability and deformity[42].

There is a controversial hypotheses whether the DMARDs increase the risk of atherosclerosis and in turn (CIMT) or that they are directly protective; causes of this are: 1) frequent changes in medications in individual RA patients, 2) changing practices in RA therapeutics over time (e.g., widespread use of methotrexate, frequent use of combination therapy, introduction of new agents), and 3) the long lead time of atherosclerosis prior to the development of symptomatic disease[55]. In the present study all RA patients were receiving at least one of DMARDs for more or less than 5 years and the results showed no effects of these DMARDs on (CIMT) (p-value 0.051) which is statistically insignificant and in consistent with those studies that showed no protective effect of DMARDs on (CIMT) as in the study of Yasuro Kumeda et al[42].

Finally, the strength of the study is to predict cardiovascular disease in the form of atherosclerosis which is the main cause of mortality in R.A. patients by measuring carotid intima media thickness by ultra sound which is easy, feasible and noninvasive method of diagnosis.

Weak points are that the study has been done in limited time and small population, therefore, larger samples and greater time might be required.

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Yazışma Adresi / Address for Correspondence:
Dr. Hawar Ali Ehsan
Sulaimaniya Medical School
Department of Rheumatology
IRAQ
e mail: haekkam@gmail.com

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