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Rheumatoid Arthritis and the Ankle-Brachial Pressure Index: Any Association?

Romatoid Artrit ve Ayak Bileği-Brakiyal Baskı Endeksi Arasında Herhangi Bir İlişki Var mı?

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ABSTRACT

Purpose: Several studies tried to assess the influence of rheumatoid arthritis (RA) on peripheral arteries and found an association with later development of intimal thickness and atherosclerosis. We tried to uncover the prevalence of subclinical peripheral vascular disease (PVD) in rheumatoid arthritis patients.

Materials and Methods: This case control-study had involved sixty patients who were diagnosed with rheumatoid. Forty age, gender, and body mass index-matched healthy individuals were selected as the control group. All participants were non-smokers, non-hypertensive, and non-diabetics and had a normal lipid profile. The presence of peripheral arterial disease was evaluated by measuring the ankle-brachial pressure index (ABPI) at the level of each artery of the lower limbs. An index of ≤0.9 was considered abnormal and a possible reflection of an underlying PVD.

Results: Twenty three (38%) out of the 60 RA patients demonstrated one or more abnormal arteries while only 3 (7.5%) out of the 40 control individuals had abnormal results (p-value <0.001). A statistically significant association was noted between abnormal ABPI and RA disease severity as indicated by C-reactive protein (P-value <0.003), ESR (P-value <0.002), and positive serum rheumatoid factor (P-value <0.01). However, age, gender, and disease duration showed no link with abnormal ABPI.

Conclusion: A higher prevalence of abnormal ABPI, and hence a possible higher incidence of subclinical atherosclerosis, was found in patients with RA. Further analytic studies are required to assess the relationship of RA with PVD.

Key Words: Rheumatoid arthritis; ankle- brachial pressure index; peripheral vascular disease

ÖZET

Amaç: Çeşitli çalışmalar, periferal arterler üzerinde romatoid artrit etkisini (RA) değerlendirmeyi araştırmış ve intimal kalınlaşmanın geç gelişimi ve ateroskleroz arasında bir ilişki bulmuştur. Biz romatoid artrit hastalarında subklinik periferik damar hastalığının (PVD) yaygınlığını ortaya çıkarmayı denedik.

Materyal ve Metod : Bu vaka kontrol çalışmasına romatoid tanısı almış 60 hasta dahil oldu. Kırk yaş, cinsiyet ve vücut kitle indeksi uyumlu sağlıklı bireyler kontrol grubu olarak seçildi. Tüm katılımcılar sigara içmeyen, hipertansif ve diyabet olmayan, normal lipid profiline sahip bireylerdi. Periferik arter hastalığı varlığı alt ekstremitenin her arter düzeyinde ayak bileği-kol basınç indeksi (ABPI) ölçülerek değerlendirildi. 0.9 ≤ indeks anormal olarak kabul edildi ve PVD' nin altında yatan olası bir yansıma olduğu düşünüldü.

Bulgular: 40 kontrol bireyin sadece 3'ünün (% 7.5) anormal sonuçları (p-değeri <0.001) var iken, 60 RA hastasının 23'ü (% 38), bir veya daha fazla anormal damar göstermiştir.
Serumda, anormal ABPI ve RA şiddeti arasındaki belirlenen istastistiksel anlamlı ilişki, RF (P-value <0.01), ESR (P-value <0.002) ve C reaktif proteni (P-value <0.003) aralarındaki ilişkiye istinaden gösterilmiştir. Ancak, yaş, cinsiyet ve hastalık süresi anormal ABPI ile bir bağlantı göstermedi.
Sonuç: Anormal ABPI prevalansının daha yüksek oluşu, ve buna bağlı olarak subklinik aterosklerozun olası yüksek insidansı RA hastalarında gözlendi. Daha ileri analitik çalışmalar PVD ile RA arasındaki ilişkiyi değerlendirmek için gereklidir.
Anahtar Kelimeler: Romatoid artrit, ayak bileği-kol basınç indeksi; periferik damar hastalığı

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease that results in continuous inflammatory synovitis, progressive joint destruction, and a higher mortality compared to the general population[1,2.] RA and atherosclerosis are two inflammatory diseases closely related; in fact, although joint symptom is the main feature of RA, atherosclerotic cardiovascular diseases (CVD) are the main source of mortality and morbidity in those patients[3,4]. Unfortunately, the majority of such patients are asymptomatic and under-diagnosed[5].

MATERIALS and METHODS

This case control study was conducted at the Sulaimaniya general teaching hospital and its outpatient clinics from March to December 2012 and involved 60 patients who had been diagnosed with RA[6] all patients had disease duration of ≥ 5 years and were receiving one or more disease modifying anti-rheumatic drugs [DMARDs]; none of them had received anti-tumor necrotic factor therapy. The latter group was compared to 40 otherwise healthy individuals who were age, gender, and body mass index-matched, who attended the outpatients' clinics because of regional pain disorders.

Patients and controls were excluded from the study if they had a history of previous and current smoking; hypertension (blood pressure ≥ 140/90 mmHg or use of antihypertensive medications)[7] hyperlipidemia (levels of total cholesterol ≥ 240 mg/dl, and/or triglycerides ≥ 200mg/dl, or the use of lipid lowering agents);[8] or diabetes mellitus (according to the World Health Organization criteria or use of antidiabetic medications)[9].

All subjects (patients and controls) underwent a battery of investigations, including complete blood count, ESR, liver function, urea and electrolytes, thyroid function, fasting blood sugar, urine examination, serum rheumatoid factor, and serum C-reactive protein. Serum rheumatoid factor was determined by latex fixation test (with agglutination) by which the results were expressed as positive or negative. The participants' ESR was assesses by Westergen method and the results were considered normal or high according to Miller's equation.

The ankle systolic blood pressures were measured at the posterior tibial and dorsalis pedis arteries in both ankles with a 8MHz Doppler ultrasound probe (Maxi Dopplex 200, Huntleigh Healthcare Limited, Cardiff, UK) and a random zero mercury sphygmomanometer attached to a contour wrapped cuff positioned 3 cm proximal to the malleoli after at least 10 min of rest in the supine position with the head at 30° from horizontal. The pulse was located with the Doppler probe facing the direction of flow and then the cuff was inflated to 20 mmHg above the audible systolic pressure. The recorded systolic blood pressure was the pressure at which the Doppler probe sounds were first audible as the cuff was deflated. The same technique was used in both brachial arteries. We calculated ABPI for each lower extremity artery by dividing its pressure by the highest of the right and left brachial pressures.

Each subject could have up to four values for the ABPI.[10]. Values of ≤ 0.9 were considered abnormal. One of the authors did the measurements.

The ankle-brachial pressure index (ABPI) was calculated by dividing the systolic blood pressure measured in the arterial conduits at the level of the ankle by the systolic blood pressure measured in the brachial artery as seen in the following equation:

Statistical Analysis:

The collected data were organized, tabulated, and statistically analyzed using Statistical Package for Social Sciences (SPSS) version 17 by an independent statistician. A comparison of continuous variables was performed by Student's t-test. Significance levels were set at *P*-value of less than 0.05 in all patients.

RESULTS

Table 1 demonstrates both groups' ages, gender, and body mass index (BMI) while table 2 displays their head-to-head comparison in terms of normal and abnormal ankle-brachial pressure index (ABPI). Tables 3, 4, and 5 show the relationship and correlation between ABPI and rheumatoid arthritis patients' age and gender, rheumatoid factor, and inflammatory markers (C-reactive protein and ESR), respectively.

Out of the 60 patients in the rheumatoid arthritis group (RAG), 54 (90%) were females while the rest (n=6, 10%) were males. In the control group (n=40), 35 (87.5%) were females and the rest (n=5, 12.5%) were males. The mean age of the RAG was 56.6 years (±10.25 years) while that of the control group was 57.2 years (±10.8 years).

In both groups combined, the ABPI was abnormal in 26 patients while it was normal in the rest (n=74).

The ABPI was abnormal (i.e., ≤ 0.9) in 23 (38.3%) patients in the RAG while it was abnormal in 3 (11.5%) patients only in the control group. Among patients with rheumatoid arthritis, there was no association between abnormal ABPI and age groups, gender, or disease duration. However, the abnormal ABPI showed a statistically significant association with seropositive rheumatoid arthritis, positive serum C-reactive protein, and high ESR.

Table 1. Age and gender of the patients and their counterpart control group.

Variables	Rheumatoid arthritis patients (n=60)		Control Group (n=40)	
	Number	Percentage	Number	Percentage
Age:				
40-49	19	32	12	30
50-59	18	30	12	30
60-69	12	20	9	22.5
≥ 70	11	18	7	17.5
Total*	60	100	40	100
Gender:				
Male	6	10	5	12.5
Female	54	90	35	87.5
Total	60	100	40	100
BMI§	25.95±4.42		7.02±5.36	

*The mean age (in years ± standard deviation) of rheumatoid arthritis group was 56.65±10.25 while that of the control group was 57.25±10.87; §expressed as Kg/m^2. ; BMI, body mass index.

Table 2: Correlation of ankle blood pressure index between rheumatoid arthritis patients (n=60) and their counterpart control group (n=40).

Variable	Studied Groups		P-value
	RA patients	Control Group	
Abnormal* ABPI	23(88.5%)	3(11.5%)	0.001
Normal ABPI	37(50%)	37(50%)	

* Defined as ABPI of ≤ 0.9.; ABPI, ankle-brachial pressure index; RA, rheumatoid arthritis.

Table 3. Correlation between ankle blood pressure index and age groups as well as gender among rheumatoid arthritis patients (n=60).

Variable	Abnormal* ABPI Number (%)	Normal ABPI Number (%)	**P values**
Age (in years) 40-49 50-59 60-69 70-79	 9(47.4%) 7(38.9%) 3(25.0%) **4(36.4%)**	 10(52.6%) 11(61.1%) 9(75.0%) **7(63.6%)**	**0.664**
Gender Male Female	 2(33.3%) 21(38.9%)	 4(66.7%) 33(61.1%)	**0.791**

Defined as ABPI of ≤ 0.9.; ABPI, ankle-brachial pressure index.

Table 4. Relationship between ankle blood pressure index with rheumatoid arthritis disease (RA) duration as well as rheumatoid factor among RA patients (n=60).

Variables			P-value
	Abnormal* ABPI Number (%)	Normal ABPI Number (%)	
Disease duration (in years) 5-14 15-24 25-35	 11(32.4%) 10(47.6%) 2(40.0%)	 23(67.6%) 11(52.4%) 3(60.0%)	0.526
Rheumatoid Factor Positive Negative	 23(44.2%) 0(0.0%)	 29(55.8%) 8(100.0%)	0.017

* Defined as ABPI of ≤ 0.9.
ABPI, ankle-brachial pressure index.

Table 5. Relationship between ankle blood pressure index and C-reactive protein as well as ESR.

Parameter			P-value
	Abnormal* ABPI Number (%)	Normal ABPI Number (%)	
CRP			
Positive	19(54.3%)	16(45.7%)	0.003
Negative	4(16.0%)	21(84.0%)	
ESR			
High	17(58.6%)	12(41.4%)	0.002
Normal	6(19.4%)	25(80.6%)	

* Defined as ABPI of ≤ 0.9.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ABPI, ankle blood pressure index.

DISCUSSION

RA is a chronic and systemic inflammatory disease which causes inflammatory synovitis and progressive joint destruction and portends a higher mortality when compared to the general population[1,2]. Females are 2.5 times more likely to be affected by this disease than males. The appearance of the disease may occur at any age but its peak frequency occurs within the fourth to fifth decades of life[11]. The overall prevalence is 1% to 2%[12].

RA and atherosclerosis are two inflammatory diseases closely related. Although the joint symptoms (painful joints, tender movements, swelling,…etc.) are the main presenting features of RA, atherosclerotic cardiovascular diseases are the main source of mortality and morbidity in those victims[3,4]. Cardiovascular events happen roughly a decade in advance in RA compared to controls[13] and life prospect of patients with RA is 3-10 years less than that of the general population[14].

PVD targets 12% to 14% of the general population according to Selvin and Erlinger[15]. According to Dormandy,[16] the prevalence of PAD is age-dependent, extends to 10% in patients above the age of 60, and 20% over the age of 75.

The highest prevalence of 29% was seen in the participants in the Peripheral arterial Awareness, Risk and Treatment New Resources for Survival (PARTNERS) program, a study of almost 7,000 patients over the age of 70, or age 60 with diabetes or current smoking[17,18].

A remarkable note is that the majority of such patients are a symptomatic and under-diagnosed. Al-Qaisi and colleagues[5] found that although intermitted claudication is the primary indicator and the first presenting symptom, the majority of the patients are either asymptomatic or do not report such symptoms to their physicians.

According to Rose criteria[19] for clinical intermittent claudication, less than 10% of them provide a reliable history consistent with the classification. History of claudication, therefore, underestimates the prevalence of PAD by a factor of 2-5, according to Crique and colleagues[20] Moreover, in the opinion of Hirsch and coworkers, diagnosing PAD based on symptoms will miss up to 90% of the disease Marrinelli et al[21] concluded that trusting feeble or absent pedal pulses will similarly undervalue the prevalence of the disease.

The ABPI has been widely accepted for confirmation of PAD and its quantification, as suggested by Al-Qaisi et al[5]. The American

Diabetes Association consensus paper defines a normal range ABPI as 09-1.3, mild disease between 0.7-0.9, moderate disease as 0.4-0.7, and severe disease as less than 0.4. An ABPI of 0.9 (and less) has a sensitivity of 95% and a specificity of 100% when weighted against angiography for detection of PVD[22].

Kimberly and coworkers[23] found that rheumatoid arthritis, particularly with extra-articular manifestations, has a significant relationship with non-cardiac vascular disease, including atherosclerosis and PAD. The risk for developing PAD remarkably increases with a number of factors including presence of systemic inflammation, concomitant vascular endothelial activation, and treatment related factors mainly use of corticosteroid[24].

Approximately, 38% of our patients demonstrated an abnormal ABPI of ≤ 0.9 while only 3% of the control group had such results. Our findings are somewhat consistent with those of Raya et al[25] who concluded that 30% of their patients with longstanding rheumatoid arthritis had abnormal ABPI in contrast to 5% of their controls.

In terms of inflammatory markers (serum CRP, ESR, and rheumatoid factor), there was a statistically significant association between abnormal ABPI and positive serum CRP, high ESR, and seropositive disease. Inmaculada del Rincón and coworkers[26] found a strong association between the aforementioned parameters and abnormal ABPI.

The current study was unable to find an association between abnormal ABPI and age (p-value<0.66), gender, or disease duration. However, Ray and colleagues[25] found a strong correlation between disease duration and abnormal ABPI in contrast to Alkaabi and coworkers[27] who found no direct link between rheumatoid arthritis disease duration and the presence and extent of lower limbs atherosclerosis and abnormal ABPI.

Recently, Ahmad and colleagues[28] concluded that RA is a pro-atherogenic state with the process of atherosclerosis initiated in the early stage of the disease. Besides the traditional risk factors, sustained inflammation contributes to atherogenesis. Miasoedova and coworkers[29] pointed out to the necessity of thorough examination of RA patients for asymptotic atherosclerosis taking account of inflammatory activity and cardiovascular disease risk factors for the optimization of early diagnostics and prediction of cardiovascular disease. Kerola et al[30] concluded that the cardiovascular risk seems to increase sooner after the RA diagnosis than previously thought. In addition to systematic cardiovascular risk assessment, patients with early RA might benefit from being targeted with stricter than conventional cardiovascular risk prevention and intervention.

Therefore and according to the recent and pertinent medical literature[31,32]. ABPI may be used as a rapid bedside screening tool to evaluate RA patients for the presence of PVD.

Limitations of the study:

1. The number of cases was relatively small and each patient underwent a single ABPI estimation by single operator.
2. Although our patients were enrolled consecutively, the randomization was not blind and several individuals were excluded because of having one or more cardiovascular risk factor (hypertension, diabetes, hyperlipidemia, and/or smoking status).
3. The impact of glucocorticoids and/or disease-modifying anti-rheumatic drugs on peripheral arties was not assessed.
4. All participants were residents of Sulaimaniya city and were Kurds (an ethnic minority in the northeast of Iraq).

Therefore, taking the aforementioned factors in consideration, our results might well have been different if the number of cases was larger; if more than 1 ABPI estimation was done and by more than one operator; if the patients were enrolled blindly; if the co-effect of immune suppressive

therapy was analyzed; and if other ethnic groups (which might carry certain genetic and life style factors) were included in the study.

CONCLUSION

A higher prevalence of "statistically" significant abnormal ABPI, and hence a possible higher incidence of subclinical atherosclerosis, was found in our patients with RA, who in particular had high ESR, positive serum CRP, and seropositive disease. Whether this finding is "clinically" significant or not, further analytic studies are required to assess the relationship of RA with peripheral vascular diseases. ABPI may be used as a rapid bed-side screening tool to assess the presence or absence of lower limbs abnormal vascular tree.

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