Association of rheumatoid arthritis disease activity, severity with electrocardiographic findings, and carotid artery atherosclerosis

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Aim
The aim was to detect specific ECG changes in rheumatoid arthritis (RA) patients as well as to study atherosclerotic changes of the carotid arteries as an indicator of cardiovascular system risk factors and to correlate findings with disease activity and severity parameters to elucidate possible associations between these variables.

Patients and methods
This study included 30 RA patients, 30 age-matched and sex-matched systemic lupus erythematosus patients and 30 age-matched and sex-matched healthy volunteers as control groups. The patients were subjected to clinical examination, assessment of disease activity score-28 (DAS28), functional disability Health Assessment Questionnaire, and laboratory and radiological assessments. ECG and measurement of the carotid intima media thickness (CIMT) by carotid ultrasound scan was also done.

Results
Ten (33.3%) RA patients had ECG abnormalities, with ST or T-wave abnormality being the most common abnormality present. RA patients had the highest frequencies of ECG abnormalities. Most ECG changes occurred in RA patients using steroids (90%). ST or T-wave abnormality in RA occurred more in patients with a higher swollen joint count, higher DAS28, and a higher patients' global health assessment. RA patients had the highest mean. The mean CIMT was significantly higher in RA patients with ECG abnormalities. There were significant positive correlations of average CIMT with DAS28, Health Assessment Questionnaire, and Simple Erosion Narrowing Score. There were significant positive correlations of mean CIMT with the level of triglycerides, cholesterol, high-density lipoprotein, erythrocyte sedimentation rate, and a highly significant correlation between mean CIMT and C-reactive protein. CIMT at a cut-off point of 0.75 mm can predict ECG abnormalities with high sensitivity and specificity.

Conclusion
ECG changes were present in 33.3% of RA patients. Increased CIMT was observed in RA patients and correlated well with disease activity and severity parameters.

Keywords:
cardiovascular risk, carotid artery atherosclerosis, electrocardiography, rheumatoid arthritis, systemic lupus erythematosus

Introduction
Rheumatoid arthritis (RA) is the most common inflammatory arthritis that affects a variety of organ systems including the cardiovascular system (CV). It is associated with disability, shortened life expectancy, and increased mortality as compared with the general population [1].

The overall life expectancy in RA is significantly reduced, with standardized mortality rates ranging from 1.28 to 3%, sometimes attributed to the increased prevalence of heart failure with preserved ejection fraction and absence of typical symptoms of heart failure in RA patients compared with non-RA patients [2].

Abnormalities detected on resting ECG in healthy adults in particular ST-segment and/or T-wave abnormalities, left ventricular hypertrophy (LVH), left axis deviation (LAD), left bundle branch block (LBBB), and right bundle branch block (RBBB) predict subsequent CVD events (e.g. sudden coronary heart disease death, nonfatal myocardial infarction, and congestive heart failure) [3].
Traditional risk factors for cardiovascular disease (CVD), such as smoking, hypertension, diabetes, and hyperlipidemia, do not fully account for the increased risk of CVD in patients with RA. In patients with RA, traditional and nontraditional risk factors play a role in the development and exacerbation of CVD [4].

Atherosclerosis is emerging as an important complication of RA, with coronary artery disease being the major cause of mortality in these patients. Both men and women with RA are twice as likely to suffer from myocardial infarction when compared with the general population [5].

Atherosclerosis can be assessed by carotid ultrasound even in subclinical stages, where plaques are detected and the intima media thickness (IMT) is measured. Increased IMT is an early sign of atherosclerosis and has been found to predict future CVD in the general population as well as in RA [6].

Aim
The aim of this study was to detect specific ECG changes in RA patients as well as to study atherosclerotic changes of the carotid arteries as an indicator of CV risk factors and to correlate the findings with disease activity and severity parameters to elucidate the possible associations between these variables.

Patients and methods
This is a cross-sectional study conducted on 90 participants attending the inpatients’ and the outpatients’ clinic of Rheumatology, Rehabilitation and Physical Medicine Department. The study was conducted according to the Helsinki Declaration and approved by the ethics committee. An informed written consent was obtained from all the patients and the control groups prior to the study.

Patients/participants in the study were classified into three groups.

Group I: including 30 RA patients fulfilling the American College of Rheumatology/European League against Rheumatism (ACR/EULAR) criteria for the diagnosis of RA [7].

Control groups (groups II and III)
Group II: 30 age-matched and sex-matched systemic lupus erythematosus (SLE) patients who met the systemic lupus international collaborating clinic (SLICC) criteria for the diagnosis of SLE [8].

Group III: 30 age-matched and sex-matched apparently healthy volunteers recruited from the hospital personnel and relatives of patients.

Patients or participants with classic CV risk factors, that is, hypertension (blood pressure 140/90 mmHg), hyperlipidemia, diabetes, autoimmune cardiac disorders, rheumatic heart disease, presence of other rheumatic or autoimmune disease or previous CV events were excluded.

All patients were subjected to the following:
(1) Full history taking (personal, complaint, present, past, and family history).
(2) Full clinical examination (including assessment of disease activity according to disease activity score-28 (DAS28) [9], assessment of functional disability using the Health Assessment Questionnaire (HAQ) [10].
(3) Laboratory assessment including complete blood picture, erythrocyte sedimentation rate (ESR), plasma glucose, C-reactive protein (CRP), rheumatoid factor titer [11], and anticyclic citrullinated peptide antibodies [12]. A complete lipid profile was obtained with the measurement of total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides.
(4) Radiological assessment: plain posteroanterior view of both hands and both feet, with assessment of radiological severity using the Simple Erosion Narrowing Score (SENS) [13].
(5) ECG and measurement of the carotid intima media thickness (CIMT) by carotid ultrasound scan for patients and healthy controls were done by A.B. (MD) who is an experienced cardiologist and one of the authors of this work.

Electrocardiography
A standard digitally recorded 12-lead resting supine ECG was performed in the Cardiology Department, Benha University Hospitals. ECG was performed by (Nihon Kohden’s Cardiofax C ECG) which recorded voltages from the heart with the 12 standard ECG leads that can be subdivided into two groups: the six-limb (extremity) leads and the six-chest (precordial) leads. ECG-CVD were defined as the presence of one or more of the following four elements (ECG-4): ST-segment and/or T-wave abnormalities, LVH, LAD, LBBB, and RBBB. ECG-5 included the same elements as ECG-4 and the Q-wave [14].
Carotid ultrasound scans
Ultrasonography was performed with a GE Vivid 7 (General Electric, Boston, Massachusetts, USA) system equipped with a 13 MHz linear array imaging probe. The right common carotid artery was examined with the patient lying supine, the head directed away from the side of interest, and the neck extended slightly. The transducer was manipulated so that the near and far walls of the common carotid artery were parallel to the transducer footprint, and the lumen diameter was maximized in the longitudinal plane. A region 1 cm proximal to the carotid bifurcation was identified, and the IMT of the far wall was evaluated as the distance between the lumen–intima interface and the media–adventitia interface. The IMT was measured on the frozen frame of a suitable longitudinal image, with the image magnified to achieve a higher resolution of detail. The IMT measurement was obtained from four contiguous sites at 1 mm intervals, and the average of the four measurements was used for the analyses. All measurements were performed by investigators without knowledge of the clinical data. Upper normal average IMT is estimated to be up to 0.8 mm with atherosclerotic plaques defined as a thickness greater than 1.5 mm as measured from the media–adventia interface [15].

Statistical methods
Data management and statistical analysis were performed using SPSS version 25 (IBM, Armonk, New York, USA). For numerical variables, comparisons between three groups were done using the analysis of variance test for normally distributed variables or Kruskal–Wallis test for non-normally distributed variables. Comparisons between the two groups were done using Mann–Whitney U-test. Categorical variables were compared using the χ²-test or Fisher’s exact test if appropriate. Receiver operating characteristic curve analysis was done for carotid IMT in the detection of cardiac affection in rheumatoid patients. Cut-off points and diagnostic indices were calculated. Correlation analysis was done using Pearson’s or Spearman’s correlation; ‘r’ is the correlation coefficient. All P values were two-sided. P values less than 0.05 were considered significant.

Results
This study included three groups:

(1) Group I: 30 adult RA patients, 27 (90%) women and three (10%) men with a mean age of 37.9±6.5 years and mean disease duration of 7.6±7.2 years.
(2) Group II: 30 SLE control patients, 28 (93.3%) women and two (6.7%) men with a mean age of 34.7±7.9 years and mean disease duration of 8.4±8.4 years.
(3) Group III: 30 apparently healthy controls, 23 (76.7%) women and seven (23.3%) men with a mean age of 38.4±11.1 years.

There were no statistically significant differences among RA patients and the control groups as regards age and sex (P>0.05).

There were six (20%) RA patients with a family history of CVD.

Extra-articular manifestations of RA patients included: normocytic normochromic anemia in 70%, subcutaneous nodules in 20%, interstitial lung disease in 6.7%, pleural effusion in 13.3%, and renal affection in 6.7%.

Electrocardiographic findings in the studied groups
A nonsignificant difference (P=1.0) is observed among all groups regarding normal and abnormal ECG findings (Fig. 1).

RA patients had the highest frequencies of ECG abnormalities with a significant difference compared with SLE controls (P=0.028) and a high significant difference compared with healthy controls (P=0.003) (Table 1).

ST or T segment abnormality was the most common findings in RA patients affecting 7/30 patients (23.3%) and 2/30 patients (6.7%) of SLE controls.

ST or T-wave abnormality occurred more in patients with a higher swollen joint count, higher DAS28, and a higher patients’ global health assessment with a statistically significant difference (P=0.04, 0.05 and 0.03, respectively). There were no significant differences of RA patients’ other clinical data regarding the presence or absence of ST or T-wave abnormality (Table 2 and Fig. 2).

ECG abnormalities associating extra-articular manifestations of RA patients occurred most frequently in patients with anemia. Patients with pleural effusion and eye affection had a higher incidence of ECG abnormalities (50% of each). None of the patients with subcutaneous nodules or pulmonary affection had ECG abnormalities.

Ninety percent of ECG changes occurred in RA patients using steroids (9/10) and 80% of changes occurred in patients using hydroquine. Leuflunomide
Carotid intima media thickness findings in the studied groups

RA patients had the highest mean CIMT with a nonsignificant difference compared with SLE.
controls and a highly significant difference compared with healthy controls ($P<0.001$) (Figs 3, 4 and Table 3).

The mean CIMT was higher in RA patients who had ECG abnormalities, with a statistically significant difference ($P=0.049$) compared with RA patients without abnormalities.

There were significant positive correlations of average CIMT with DAS28 ($r=0.468$, $P=0.01$), HAQ ($r=0.431$, $P=0.02$), SENS ($r=0.453$, $P=0.01$), and a nonsignificant correlation with age ($r=0.113$, $P=0.55$), disease duration ($r=0.329$, $P=0.08$), morning stiffness ($r=0.304$, $P=0.10$), BMI ($r=0.296$, $P=0.11$), TJC ($r=0.224$, $P=0.23$), SJC ($r=0.325$, $P=0.08$), and patients’ global health assessment ($r=0.191$, $P=0.31$).

There were significant positive correlations of average CIMT with the level of triglycerides ($r=0.389$, $P=0.03$), cholesterol ($r=0.602$, $P<0.001$), HDL ($r=0.381$, $P=0.04$), ESR ($r=0.440$, $P=0.02$), and a highly significant correlation between average CIMT and CRP ($r=0.490$, $P<0.01$) and a nonsignificant correlation with hemoglobin ($r=0.185$, $P=0.33$), WBCs ($r=0.1$, $P=0.60$), platelets ($r=-0.166$, $P=0.38$), and low-density lipoproteins ($r=0.198$, $P=0.33$).

ECG abnormalities in RA patients can be predicted at a cut-off point of 0.75 mm of CIMT with a sensitivity of 70% and a specificity of 65%; (Table 4 and Fig. 5).

**Discussion**

CVD has been described as the main cause of premature mortality and sudden death in patients with RA. This is a result of the process of accelerated atherosclerosis [12]. It has been shown also that an increased risk of CVD is present even in preclinical stages and in very early RA [16].

Abnormalities detected on resting ECG in healthy adults are associated with an increased risk for subsequent CVD events. In a systematic review, Chou et al. [3] found that resting ECG abnormalities (ECG–CVD 4-elements), in particular
ST-segment and/or T-wave abnormalities, LVH, LAD, LBBB, and RBBB, were associated with subsequent CVD events (e.g., sudden coronary heart disease death, nonfatal myocardial infarction, and congestive heart failure).

In our study, ECG abnormalities associated extra-articular manifestations of RA patients occurred most frequently in patients with anemia. Patients with pleural effusion and eye affection had a higher incidence of ECG abnormalities (50% of each). None of the patients with subcutaneous nodules or pulmonary affection had ECG abnormalities.

In our study, normal ECG findings were present in 66.7% of RA patients, (90%) of the SLE control group and 96.7% of the healthy controls. ECG abnormalities occurred in 33.3% of RA patients, 13.3% of the SLE control group as well as one of the apparently healthy controls. There was a nonsignificant difference ($P=1.0$) among these groups.

RA patients had the highest frequencies of ECG abnormalities with a significant difference compared with SLE controls ($P=0.028$) and a high significant difference compared with healthy controls ($P=0.003$).

ST-segment or T-wave changes were the most common abnormal findings of RA patients present in 70%, while 30% had LVH. Sixty-six (66.7%) of the SLE control patients had ST-segment or T-wave abnormality and 33.3% had LBBB. One/1 of apparently healthy controls had ST-segment or T-wave abnormality (100%).

Comparable to our results, Shenavar-Masooleh et al. [17] conducted a study on 100 RA patients and found that 32% had abnormal ECG findings. The most abnormal findings were ST-segment and T-wave changes which were similar as reported in our patients; however, they occurred as 46.9% of abnormalities. Moreover, sinus tachycardia and low voltage were observed in 3.1% each, premature

<table>
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<th>Table 3 Comparison between average carotid intima media thickness regarding ECG abnormalities of rheumatoid arthritis patients</th>
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<td>Positive ECG finding ($n=10$)</td>
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<td>Average CIMT (mm)</td>
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<td>0.826±0.18</td>
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$P<0.05$, significant difference.

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<th>Table 4 Sensitivity and specificity of carotid intima media thickness in the prediction of electrocardiographic abnormalities in rheumatoid arthritis patients</th>
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<td>AUC (95% CI)</td>
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<td>0.723 (0.541–0.904)</td>
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95% CI, 95% confidence interval; AUC, area under the curve.

An ultrasonogram of a measured carotid artery intima media thickness of 0.85 mm in a female rheumatoid arthritis patient aged 41 years.

Figure 4
ventricular tachycardia in 6.2%, axis deviation and poor R progression in 9.3% each, branch block in 12.5%, and pulmonary P in 15.6% of abnormalities.

Another study by Dodo-Siddo et al. [18] found that among RA patients there were a significant number of LVH (46.6%). From the analysis, it appeared that the existence of these abnormalities correlated with age. Also, LAD was found in 16.44% of their patients. Twenty-six patients had signs consistent with ischemia and/or myocardial injury or a rate of 35.61%.

On the other hand, Coşkun et al. [19], in their study on 100 RA patients, found ECG abnormalities in only 7% of patients, none of them had ST or T segment abnormality.

Similarly, in the Geraldino-Pardilla et al. [20] study, 44% of the patients with SLE had nonspecific ST-segment and T-wave abnormalities (95% confidence interval: 32–56%) compared with 17% (10–24%) of the patients with RA (OR=3.8; 95% confidence interval: 1.8–7.7; P=0.0001).

Coşkun et al. [19] also stated that when RA patients with ECG abnormalities were compared with those without ECG abnormalities, in terms of age, disease duration, ESR, CRP, rheumatoid factor, immunoglobulin (Ig)G, IgA, IgM, C3, C4, TC, and triglyceride levels, those patients with ECG abnormalities were significantly older (P<0.05), but there was no significant difference in other parameters (P>0.05).

These results coincided with our results, where ECG abnormalities occurred in older patients with a longer disease duration or morning stiffness, and higher body mass index, DAS28, patient’s global health assessment or HAQ, with no significant differences of RA patients’ clinical data regarding the presence or absence of ECG abnormalities.

Considering the laboratory and radiological data in our study, there were no significant differences of RA patients’ laboratory and radiological findings regarding the presence or absence of ECG abnormalities.

It has been shown that a high level of CRP in RA is an independent predictor for CV morbidity and mortality [21].

Lazzerini et al. [22] indicated that the association between inflammatory marker levels, such as CRP and interleukin-6, with ECG abnormalities has been previously described in patients with RA, which was not evident in this work.

Analyzing our results regarding ST-segment or T-wave abnormality, we found that it occurred more in patients with a higher swollen joint count, higher DAS28 and a higher patients’ global health assessment with a statistically significant difference (P=0.04, 0.05 and 0.03, respectively).

There were no significant differences of RA patients’ other clinical data, laboratory and radiological findings regarding the presence or absence of ST-segment or T-wave abnormality.

Sharma et al. [23] suggested a CV-protective effect for medications such as hydroxychloroquine, methotrexate (MTX), and antitumor necrosis factor inhibitors.

Other evidence-based studies highlight the cardioprotective effects of disease modifying anti-rheumatic drugs (DMARDs) particularly MTX and biologics. Choi et al. [24] have demonstrated that MTX-treated patients had a 70% reduction in CV mortality compared with those who did not receive a DMARD. However, the role of corticosteroids, COXIBs, and most NSAIDS remains controversial.

However, this was not evident in our study, where 90% of ECG changes occurred mostly in RA patients on corticosteroids and 80% of changes occurred in patients on hydroquinine. The least common changes (20%) occurred in patients on leuflunomide. Fifty percent of changes affected patients receiving MTX. There...
was a nonsignificant difference for the presence or absence of these changes between patients receiving the same DMARD.

Lipid levels appear to be altered as a result of RA disease activity. Data on TC and low-density lipoprotein cholesterol (LDL-C) levels in RA patients are conflicting: some studies demonstrate similar or lower levels of TC, while others demonstrate increased levels of TC and LDL-C in patients with early RA [25].

In the current study, the mean level of cholesterol was lower in RA patients than SLE controls with a nonsignificant difference between them (\( P=0.593 \)), but a significant difference compared with healthy controls (\( P=0.022 \)). The mean level of LDL was highest in RA patients with a nonsignificant difference compared with SLE controls (\( P=0.1 \)) and a high statistically significant difference compared with healthy controls (\( P=0.001 \)).

These results agreed with the study of Liao et al. [26] in which the mean TC was lower in RA compared with non-RA, but disagreed in that the LDL-C was also lower in RA compared with non-RA.

The study of Saigal et al. [27] that was carried out on RA patients reported that serum triglyceride was significantly lower in the cases as compared with the control group (\( P<0.008 \)). No significant difference was observed in the levels of TC, LDL, and HDL cholesterol in the two groups.

Wang et al. [28] found that TC and LDL were significantly lower in the RA group (\( P<0.05 \)) compared with the healthy control group.

A systemic review and meta-analysis of several studies encompassing the entire spectrum of rheumatic diseases had observed a significantly increased CIMT in these patients as compared with matched healthy individuals [29].

In this study, there were high statistically significant differences in the mean CIMT of RA and SLE patients as compared with the healthy controls (\( P<0.001 \)), while a nonsignificant difference existed between the two diseases (\( P>0.05 \)).

Similar to our study, in the RA study of Gauri et al. [30] that was carried out on 100 participants, the mean CIMT of the study group participants was significantly greater (\( P<0.001 \)) than that of the controls group. This was also reported in the Patel et al. [31] study.

Patel et al. [31] found that the mean values of the common CIMT for mild, moderate, and severe activity subgroups when compared with each other were found to be statistically significant, suggesting a correlation between disease activity at a particular time and CIMT. This was comparable to our results. Similar results were found by Carroti et al., Singh et al., and Gauri et al. [5,30,32]. However, contradictory observations have been presented by Jonsson et al. [33] and Roman et al. [34].

Lloyd-Jones et al. [35] stated that minor and major ECG abnormalities are established, independent risk markers for incident CV events. Their association with subclinical atherosclerosis has been postulated but is not clearly defined as indicated by the presence of coronary artery calcification (CAC) or the amount of common CIMT.

When we studied the mean CIMT regarding ECG abnormalities, the average CIMT was higher in RA patients who had ECG abnormalities, with a statistically significant difference (\( P=0.049 \)) compared with RA patients without abnormalities.

Increased CIMT was independent of traditional CV risk factors but was related to RA disease activity, duration, and severity [36].

This approved with our work, where there were significant positive correlations of average CIMT with DAS28 (\( r=0.468, P=0.01 \)), HAQ (\( r=0.431, P=0.02 \)), and SENS (\( r=0.453, P=0.01 \)), while correlations of other parameters such as sex, age, disease duration, duration of morning stiffness, and BMI, were insignificant correlations (\( P>0.05 \)).

Also, in agreement with our study, the study of Verma et al. [37] on Indian RA patients found that there were significant positive correlations of CIMT with age, DAS28, and HDL. However, there was nonsignificant correlation of CIMT with disease duration and BMI.

In this study, there were significant positive correlations of average CIMT with triglycerides (\( r=0.389, P=0.03 \)), cholesterol (\( r=0.602, P<0.001 \)), HDL (\( r=0.381, P=0.04 \)), and ESR (\( r=0.440, P=0.02 \)), while there was a highly significant correlation between average CIMT and CRP (\( r=0.490, P<0.01 \)).

On the contrary, Saigal et al. [27] found nonsignificant correlations of CIMT with DAS28, ESR, triglycerides, TC, and LDL levels.
This difference in results might be due to the fact that DAS28 and ESR levels often fluctuate in chronic inflammatory diseases and their measurement at a single point can show the inflammatory burden at that point of time only.

Conclusion and recommendation
From our study we concluded that the ECG changes were quiet prevalent in RA, being present in 33.3% of patients. Association of RA with ST or T segment abnormalities specifically needed more clarification.

A higher prevalence of increased CIMT was observed in RA patients that correlated well with the disease activity parameters. Increased CIMT in RA showed a higher sensitivity and specificity for the prediction of ECG abnormalities. Appraisal of CV risk factors in RA, even by a simple ECG test may be important for decisions regarding management and treatment plans.

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Conflicts of interest
There are no conflicts of interest.

References


