EGYPTIAN RHEUMATOLOGY & REHABILITATION

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Table of contents

Original articles

71 Carotid artery atherosclerosis and ECG changes in patients with systemic lupus erythematosus: relation to disease activity and severity
Samia M. Abdel-Monem, Sahar S. Ganeb, Rasha M. Fawzy, Ahmed M. Bendary, Zeinab N. Elhawary

78 Outcome of intensive rehabilitation following single-event multilevel surgery for crouch gait in children with cerebral palsy

85 Premature ovarian failure in systemic lupus erythematosus patients: is it related to cyclophosphamide treatment?
Rasha M. Ghaleb, Khaled A Fahmy

92 Neuromuscular ultrasound in ulnar neuropathy at the elbow: correlation with electrodagnostic studies
Esraa Muhammad Bastawy, Naglaa Ali Gad Allah, Ola Abd El Nasser, Eman Ahmed Tawfik

101 Clinical significance of interleukin 27 serum concentration in patients with systemic sclerosis: relation to clinical, laboratory, and radiological parameters
Waleed A. Hassan, Gamal A. Hamaad, Emtethal A. Sayed, Mona M. El Behisy, Manal K. Gomaa

108 Relation of ischemia-modified albumin to disease manifestations and activity in Egyptian patients with Behçet's disease
Nermeen A. Fouad, Tarek I. Ahmed, Olfat G. Shaker, Omayma O. Abdelaleem

113 Ultrasonographic features of tibialis posterior tendon in rheumatoid arthritis patients with pes planovalgus

121 Patellar tendon ultrasonographic properties and lower limb function in rheumatoid arthritis patients
Samia Abd El Hamid Abd El Megid, Salwa Saeid El Gendy, Hussein Abd El Aziz Yassin, Marwa Mohamed Mohamed Ali Abd El Rahim, Mai Abd El Halim Abd El Razik Moussa

132 Combined (physical and medical treatment) therapy versus physical treatment alone and medical treatment alone in the management of chronic pelvic inflammatory disease
Dalia S. Saif, Dina S. Fotoh, Reem M. EL Kholy, Dalia I. Morsi, Heba M. Farag
Carotid artery atherosclerosis and ECG changes in patients with systemic lupus erythematosus: relation to disease activity and severity

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Aim
This study aimed to detect atherosclerotic changes in the carotid arteries of systemic lupus erythematosus (SLE) patients as an indicator of cardiovascular risk factors and to correlate the findings with disease severity and activity parameters as well as to study specific ECG changes in these patients to elucidate possible associations between these variables.

Patients and methods
This study included 30 SLE patients who met the Systemic Lupus International Collaborating Clinics (SLICC) criteria (group I), 30 rheumatoid arthritis (RA) patients diagnosed according to the American College of Rheumatology/European league against rheumatism (EULAR) 2010 criteria (group II), and 30 apparently healthy volunteers age and sex matched to the SLE patients’ group (group III). All patients were subjected to full history taking, thorough clinical examination, assessment of disease activity using the Systemic Lupus Erythematous Disease Activity Index (2 K) score and assessment of damage by the SLICC/American College of Rheumatology Damage Index (SDI). Laboratory investigations included: complete blood count, erythrocyte sedimentation rate, lipid profile, immunological profile (antinuclear antibodies, anti-double-stranded DNA antibody, anticardiolipin antibody, and complements C3 and C4). The right common carotid artery was scanned by ultrasound and the average of carotid intima media thickness (CIMT) was calculated (mean of four readings) for all participants participating in the study. ECG was also done for all participants.

Results
The mean CIMT was higher in RA patients (0.71±0.194 mm) with a nonsignificant difference compared with SLE patients (0.68±0.197 mm) and a high statistically significant difference ($P<0.001$) compared with healthy controls (0.34±0.09 mm). There was no statistically significant correlation of the mean CIMT (mm) with SLICC damage index ($P=0.09$) and disease activity score ($P>0.05$). Abnormal ECG findings were observed in 3/30 SLE patients (10%), 10/30 RA patients (33.3%), and one/30 healthy control (3.3%), with statistically significant difference ($P<0.03$) among groups. The presence or absence of abnormal ECG findings showed statistically insignificant differences regarding patients’ disease activity and mean CIMT.

Conclusion
Although ECG changes were present in 10% of our SLE patients, association of specific ECG changes could not be confirmed. A greater prevalence of increased CIMT was observed in SLE patients, emphasizing the important role of this disease in the development of premature atherosclerosis which did not correlate with disease activity or severity parameters.

Keywords:
carotid artery atherosclerosis, ECG, systemic lupus erythematosus

Introduction
Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterized by autoantibody production and variable organ system manifestations, associated with increased risk of cardiovascular disease (CVD) [1]. SLE can affect any layer of the heart and cause endocarditis, myocarditis, and pericarditis which are generally reflected by symptoms and functional disability [2]. Despite improvements in survival in the past decades, mortality due to CVD in SLE remains unchanged [3].
SLE disease is an independent risk factor for CVD [4]. This makes traditional CV risk stratification scores developed for the general population less accessible in identifying patients with SLE at high risk for CVD. Consequently, there is a growing interest in improving CV risk stratification in SLE [5].

Subclinical atherosclerosis can be detected using several modalities, such as carotid intima media thickness (CIMT), flow-mediated dilation, coronary artery calcification by computed tomography scan, and myocardial perfusion using single-photon emission computed tomography [6]. CIMT assessed by B-mode ultrasound is a simple and noninvasive inexpensive tool that can be used to identify subclinical atherosclerotic disease; it is an independent predictor of future CV risk [7].

ECG is a useful universally available noninvasive inexpensive tool. Screening for resting ECG abnormalities in asymptomatic adults found that resting ECG serves as predictors of CV events and might help better guide use of risk-reduction therapies [8].

**Aim**

This study aimed to detect atherosclerotic changes in the carotid arteries of SLE patients as an indicator of CV risk factors and to correlate the findings with disease activity and severity parameters as well as to study specific ECG changes in these patients to elucidate possible associations between these variables.

**Patients and methods**

This study included:

Group I: 30 SLE patients who met the Systemic Lupus International Collaborative Clinics (SLICC) SLE Criteria [9].

Group II: 30 age-matched and sex-matched rheumatoid arthritis (RA) control patients diagnosed according to the American College of Rheumatology/EULAR 2010 criteria [10].

Group III: 30 age-matched and sex-matched apparently healthy control volunteers.

All patients were selected from the inpatients’ and the outpatient’s clinic of the Rheumatology, Rehabilitation and Physical Medicine Department, Benha University Hospitals. Controls were recruited from the hospital personnel and relatives of other patients.

The study was conducted according to the Helsinki Declaration and approved by the ethics committee of Benha Faculty of Medicine. An informed written consent was obtained from all the patients and control groups prior to the study.

Patients and controls were excluded from the study if their age is less than 16 years, had diabetes mellitus, hyperlipidemia on statins, hypertension, BMI greater than 25, smoking, previous history of CV events, and other autoimmune or inflammatory diseases.

All SLE patients were subjected to full medical history taking and thorough clinical examination. The SLE Disease Activity Index 2000 (SLEDAI 2 k) [11] and the SLICC/American College of Rheumatology Damage Index (DI) [12] were used to assess disease activity and damage, respectively.

Laboratory investigations included complete blood count, erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein, antinuclear antibodies, C3, C4, immunoglobulin G (IgG) antibodies to dsDNA, IgG/IgM anticardiolipin antibodies, complete urine analysis, renal function tests, 24 h proteins in urine, and fasting blood glucose. Total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides were evaluated in blood samples taken in the morning after 14 h of fasting using standard enzymatic methods with an autoanalyzer.

Measurement of the CIMT by carotid ultrasound scan and ECG for patients and healthy controls were done by an experienced cardiologist who is one of the authors of this work.

**Ultrasonographic study**

Ultrasonography was performed with a GE Vivid 7 system (GE Healthcare, Milwaukie, WI) 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 examination, and the neck extended slightly. The transducer is manipulated so that the near and far walls of the common carotid artery are 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 intima media thickness of the far wall was evaluated as the distance between the lumen–intima interface and the media–adventitia interface. The CIMT measurement is obtained from four contiguous sites at 1 mm intervals, and the average...
of the four measurements is used for the analyses. The performing investigator was blinded to all clinical data. Upper normal average intima media thickness is estimated to be up to 0.8 mm with plaque defined as a thickness greater than 1.5 mm as measured from the media–adventitia interface to the intima–lumen interface [13].

ECG
A standard digitally recorded 12-lead resting supine ECG was performed in the Cardiology Department, Benha University Hospitals. It was performed by Nihon Kohden’s Cardiofax C ECG (Nihon Kohden’s, Japan). ECG-CVD were considered if there was one or more of the following four elements (ECG-4): 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). ECG was interpreted by one of the authors who was blinded to the patients’ data.

Statistical analysis
Data were tabulated, coded, and then analyzed using the computer program SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, Illinois, USA) version 22. Descriptive statistics were calculated for the data in the form of mean±SD and number and percentage. Analysis of variance test was used to compare between more than two groups of numerical (parametric) data, for continuous nonparametric data. Kruskal–Wallis test was used for intergroup analysis; post-hoc test (LSD, Least significant difference) was used to compare between every two groups; and Student’s t-test was used to compare between two groups of numerical (parametric) data. Mann–Whitney test was used for intergroup analysis; χ²-test was used for comparison of categorical data. Correlation coefficient (r) was used to detect the association between different variables. A P value less than 0.05 was considered statistically significant and a P value less than 0.0001 was considered highly significant in all analyses.

### Results
This study included 30 SLE patients, 28 (93.3%) women and two (6.7%) men, whose ages ranged between 21 and 53 years (mean±SD 34.7±7.9 years), and their disease duration ranged between 2 months and 37 years (mean ±SD 8.4±8.5 years). There were 30 RA control patients, 27 (90%) women and three (10%) men whose ages ranged between 20 and 50 years (mean±SD 35.9±6.8 years) and their disease duration ranged between 1 and 26 years (mean±SD 7.6±7.2 years) and 30 apparently healthy control volunteers, 26 (86.6%) women and four (13.3%) men whose ages ranged between 20 and 59 years (mean±SD 34.9±8.8 years). All three groups had nonsignificantly different ages (P>0.05) and sex (P>0.05) compared with each other.

Clinical features of SLE patients were malar rash in 25 (83.4%) patients, photosensitivity in 18 (60%) patients, oral ulcers in 20 (66.7%) patients, arthritis and/or arthralgia in all of the patients (100%), pulmonary manifestations in the form of pleuritis and/or effusion in 10 (33.3%) patients, neurological manifestations in the form of headache, seizures were found in three (10%) patients, 23 (76.7%) patients had lupus nephritis based on the presence of proteinuria, active urine sedimentation, or biopsy-proven renal disease.

### CIMT findings in the studied groups
SLE patients had a CIMT that ranged from 0.25 to 1.1 mm thickness (mean±SD 0.68±0.197 mm), only 10 out of 30 SLE cases showed an increased CIMT of above 0.8 mm, while RA patients had a CIMT ranged from 0.39 to 1.2 mm thickness (mean±SD 0.71±0.194 mm), only 12 out of 30 RA cases showed an increased CIMT of above 0.8 mm (Table 1).

SLE patients had a nonsignificant difference compared with RA controls (P>0.05) and a significant difference compared with healthy controls (P<0.05).

There were no statistically significant correlations of mean CIMT values with patients’ ages (r=0.18;

### Table 1 Comparison among systemic lupus erythematosus patients and the control groups regarding the mean carotid intima media thickness

<table>
<thead>
<tr>
<th>Variables</th>
<th>SLE patients (n=30) (mean±SD)</th>
<th>RA controls (n=30) (mean±SD)</th>
<th>Healthy controls (n=30) (mean±SD)</th>
<th>F test</th>
<th>P value</th>
<th>Post-hoc analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIMT (mm)</td>
<td>0.68±0.197</td>
<td>0.71±0.194</td>
<td>0.34±0.09</td>
<td>44.2</td>
<td>&lt;0.001**</td>
<td>P₁&lt;0.05 P₂&lt;0.05* P₃&lt;0.05*</td>
</tr>
</tbody>
</table>

CIMT, carotid intima media thickness; P₁, between SLE and RA; P₂, between SLE and healthy control; P₃, between RA and healthy control; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus. **P<0.001, highly significant. *P<0.05, significant. P>0.05, nonsignificant.
There was no correlation between mean CIMT and SLE patients’ sex ($P=0.9$), family history of premature CVD, positive anti-dsDNA ($P=0.9$), or positive CRP ($P=0.5$).

There were no statistically significant correlations of mean CIMT values with TC ($r=0.08; P=0.68$), HDL ($r=-0.33; P=0.08$), and LDL ($r=0.07; P=0.73$), while there was a statistically significant correlation with the level of triglycerides ($r=0.52; P=0.00$). Other laboratory parameters also showed nonsignificant correlations (hemoglobin%, red blood cells, white blood cells, platelets, ESR, serum urea, serum creatinine, 24 h protein in urine, C3, and C4).

There were no statistically significant differences of mean CIMT among SLE with different disease activity scores ($P>0.05$) as well as a nonsignificant correlation between mean CIMT and SLICC damage index ($r=0.31, P=0.09$).

There were no statistically significant ($P>0.05$) correlations of mean CIMT regarding the duration of drug used (prednisone, chloroquine, and azathioprine).

### ECG findings in the studied groups

Two/30 SLE patients (6.7%) had ST-segment abnormalities, one (3.3%) patient had RBBB; the remaining 27 (90%) patients had a normal ECG study. None of the SLE patients had left ventricula LVH, LAD or the Q-wave, while 7/30 RA patients (23.3%) had ST-segment abnormalities, three (10%) patients had LVH; the remaining 20 (66.6%) patients had a normal ECG study. None of the RA patients had LBBB, RBBB, LAD, or the Q-wave (Table 2 and Fig. 1).

ECG abnormalities in SLE patients were nonsignificantly different compared with healthy controls ($P=0.028$) and were significantly different compared with RA controls who had the highest frequencies of ECG abnormalities.

Comparative studies of ECG findings in the SLE group regarding patients age (years), BMI (kg/m$^2$),

### Table 2 Comparisons among the studied groups regarding ECG findings

<table>
<thead>
<tr>
<th>Variables</th>
<th>SLE ($n=30$)</th>
<th>RA controls ($n=30$)</th>
<th>Healthy controls ($n=30$)</th>
<th>Stat-test</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal ECG findings</td>
<td>3 (10)</td>
<td>10 (33.3)</td>
<td>1 (3.3)</td>
<td>11.4</td>
<td>0.003*</td>
</tr>
<tr>
<td>Normal ECG findings</td>
<td>27 (90)</td>
<td>20 (66.6)</td>
<td>29 (96.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

**Figure 1**

Comparisons among the studied groups regarding ECG findings.
disease duration, disease activity, and mean CIMT revealed statistically insignificant differences \((P=0.05)\).

Comparisons of ECG findings regarding laboratory data of SLE patients revealed nonsignificant differences except for ESR \((P=0.01)\).

There were nonsignificant differences \((P>0.05)\) regarding the occurrence of normal or abnormal ECG changes in relation to the durations of all the medications used.

There was no significant difference of mean CIMT between patients with and without ECG changes (Fig. 2).

**Discussion**

SLE is associated with an increased risk of CVD. Measurement of the CIMT is such a marker that can be used to diagnose subclinical atherosclerotic disease. The ECG is a noninvasive screening tool for the evaluation and identification of patients at increased risk for CV events with a relatively minimal cost burden. Dyslipidemia is defined as any alteration in the basic lipid profile that affects about one-third of SLE patients at the time of diagnosis and almost 60% after 3 years [14].

Eesdaile et al. [15] reported that the excess of CV events in SLE cannot be explained only by the traditional risk factors but also arises from the underlying disease and/or its treatment.

Regarding our results, there was a statistically significant difference \((P<0.05)\) between the mean CIMT of SLE patients and the healthy control group \((0.68 \pm 0.197 \text{ vs. } 0.34 \pm 0.09)\) respectively, while there was a nonstatistically significant difference \((P>0.05)\) between the mean CIMT of the SLE patients’ group and the RA control group \((0.68 \pm 0.197 \text{ vs. } 0.71 \pm 0.194)\), respectively. These results are in agreement with those of de Leeuw et al. [16], El Saadany et al. [17], and Uslu et al. [18]. Inflammation plays a role in the development of the atherosclerotic lesion, interaction between traditional risk factors, antibody-mediated vascular injury, and immune dysregulation from the underlying disease, all play vital roles in endothelial dysfunction which accelerates the atherosclerotic development in SLE [19].

We also found that, there was a statistically significant correlation of mean CIMT values with the level of triglycerides \((r=0.52; \ P=0.004)\), nonstatistically significant correlations \((P>0.05)\) with TC \((r=0.08; \ P=0.68)\), HDL \((r=-0.33; \ P=0.08)\) and LDL \((r=0.07; \ P=0.73)\). This is in agreement with the results of Sozeri et al. [20] and Kiani et al. [21].

**Figure 2**

Comparison of mean carotid intima media thickness of systemic lupus erythematosus patients regarding ECG findings \((P=0.9)\).
Nikpour et al. [14] demonstrated that lipid values may change over time, reflecting changes in disease activity and therapy with antimalarials which exhibit a favorable effect on the lipid profile.

In this study, there were insignificant correlations ($P>0.05$) of mean CIMT values with patients’ ages ($r=0.18$), sex ($P=0.9$), lupus disease duration ($r=0.23$), and patients family history of premature coronary artery disease ($P=0.5$) in first-degree relatives before the age of 65 years for women and 55 years for men.

Khairy et al. [22] found that SLE cases with a history of CVD had a significantly increased CIMT compared with both those without CVD history or healthy controls ($P<0.001$). They explained in their study that there was a significant difference regarding CRP and ESR between the two SLE groups. They also found a significant difference regarding levels of both lupus anticoagulants ($P=0.01$), ACL antibodies ($P=0.006$), higher cumulative prednisone dose ($P=0.4$), and SLEDAl score (0.001) compared with SLE controls (without CVD).

Insignificant correlations of the disease activity score (SLEDAl 2k) and SLICC damage index were found among SLE patients regarding the mean CIMT ($P=0.9, 0.09$, respectively). All correlations of the laboratory parameters (hemoglobin, red blood cells, white blood cells, platelets, ESR, serum urea, serum creatinine, 24 h urine protein, C3 and C4) as well as the duration of drugs used with CIMT in the SLE patients’ group I were nonsignificant ($P>0.05$). This was in agreement with Falaschi et al. [23] and Kiani et al. [21] studies; meanwhile, it did not coincide with both Kisiel et al. [24] and Hassan et al. [25]. This could be explained by a small number of SLE patients in our study and 93.3% of our cases were women which had milder disease severity than men. Al Rayes et al. [26] reported that ECG-CVD abnormalities (ECG-CVD) are predictive of subsequent CVD events in the general population and that SLE patients are vulnerable to CVD.

This work showed a total of 3/30 (10%) SLE patients having abnormal ECG findings compared with 10/30 (33.3%) RA patients and one (3.3%) of the normal control group, with a statistically significant difference ($P<0.003$). However, Bourrée-Tessier et al. [3] and Myung et al. [27] detected a higher prevalence of resting ECG abnormalities in their SLE patients (58.2 and 57.4%, respectively). This may be explained by the difference in sample size and lack of hospital database as we investigated only 30 SLE patients in our study, but they collected 558 SLE patients from 2011 to 2015 as a part of their regular databank protocol.

In our study, a higher prevalence of nonspecific ST-T abnormalities occurred in 6/10 (23.3%) of RA patients compared with 2/3 (6.7%) of SLE patients. This was not in agreement with Geraldino-Pardilla et al. [6] who observed that SLE disease has a higher prevalence of nonspecific ST-T abnormalities (56 vs. 17%; $P<0.0001$) compared with RA, despite the older age, in a higher percentage of men in the RA group. This may be explained by the difference in sample size and races, as our study included only Egyptian patients.

Comparative studies of ECG findings among SLE patients regarding patients’ data, disease activity scores, and average CIMT measurements revealed statistically insignificant differences ($P=0.05$) which are in accordance with Geraldino-Pardilla et al. [6] results. However, Al Rayes et al. [26] reported a higher prevalence of ECG-CVD in patients with a longer SLE disease duration, increased patients’ ages, active SLE disease, and damage while treatment of hyperlipidemia was protective against such events.

Conclusion
Ten out of 30 SLE (33.3%) cases showed an increased CIMT of above 0.8 mm of CIMT, emphasizing the important role of this disease in the development of premature atherosclerosis. ECG changes were present in 10% of our SLE patients; meanwhile, the association of specific ECG changes could not be confirmed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
Carotid artery atherosclerosis and ECG changes in SLE patients

Abdel-Monem et al


Outcome of intensive rehabilitation following single-event multilevel surgery for crouch gait in children with cerebral palsy


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Background
Crouch gait is one of the most common gait patterns in ambulatory children with cerebral palsy (CP) and is contributed by several factors. The literature reports wide variations in surgical practice and rehabilitation programs following single-event multilevel surgeries.

Objective
To evaluate the outcome of rehabilitation after single-event multilevel orthopedic surgery for crouch gait in children with CP.

Patients and methods
A total of 20 children with bilateral spastic CP and walked with a crouch gait, with gross motor function classification system levels II, III, and IV, were subjected to single-event multilevel surgery. Ten (20 limbs) patients were men and eight (14 limbs) were women. Their age ranged from 5.5 to 19 years. To assess the outcome of our rehabilitation program, we used clinical couch examination parameters, functional mobility scale, and instrumented three-dimensional gait analysis. Rehabilitation program included preoperative and postoperative rehabilitation at 1-year postoperatively.

Results
Highly statistically significant improvements in clinical parameters, which include hip abduction, femoral anteversion, fixed flexion deformity, popliteal angle, and extension lag, were demonstrated (P<0.01), whereas tibial torsion showed a statistically significant improvement (P<0.05). Functional mobility scale at 5, 50, and 500 m improved in 10 (55.6%) cases, 13 (72.2%) cases, and 11 (61.1%) cases, respectively. Instrumented gait laboratory parameters, namely, stride length, crouch angle at initial stance, and peak knee flexion in mid-swing, showed improvement but did not reach statistical significance.

Conclusion
The rehabilitation program we offered improves clinical and functional mobility of children with CP with crouch gait. Thus, it is viewed as an important contributor to the overall outcome together with multilevel orthopedic surgery.

Keywords:
cerebral palsy, gait, multilevel, rehabilitation

Introduction
Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occur in the developing fetal or infant brain [1]. Ambulatory children with CP present with different gait patterns caused by spasticity and contractures with subsequent limited range of motion (ROM), leading to loss of functional abilities. Crouch gait is one of the most common gait patterns in children with ambulatory CP [2]. Rodda et al. [3] described five patterns of gait in spastic diplegic patients based on the pelvis, hip, knee, and ankle position during stance. With a definition of crouch gait as knee flexion throughout stance larger than 20°, the ankle is excessively dorsiflexed and the hip is excessively flexed during stance. The pelvis is in the normal range or tilted posteriorly [3]. Children may demonstrate crouch gait because of weakness of hip and knee extensors and ankle plantar flexors as well as contracted hamstrings and hip flexors [4]. Once the crouch gait reaches a certain level of severity in the child, the degree of knee flexion and associated symptoms may progress rapidly because of high stresses at the knee and failure of the knee extensor mechanism. Knee pain, patella alta, and fragmentation or fracture of the inferior pole of the patella all have been documented in this clinical setting [5].

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Single-event multilevel surgery (SEMLS) improves the likelihood of achieving sagittal plane balance, reduces the need for repeated anesthesia, episodes of hospitalization, and requires only one major period of rehabilitation with reduction of the cost [6]. A systematic review of SEMLS reported wide variations in surgical practice and rehabilitation. It is the postoperative rehabilitation that makes children functionally ‘better’ [7]. This study aimed to evaluate the effect of rehabilitation after single-event multilevel orthopedic surgery for crouch gait in children with CP.

**Patients and methods**

This was a cross-sectional prospective study that initially included 20 patients who had bilateral spastic CP and walked with a crouch gait, and who underwent SEMLS; all cases were operated upon and followed up at the authors’ institutions.

**Inclusion criteria**

The following were the inclusion criteria:

1. Ambulatory children more than or equal to 5 years of age and adolescents with bilateral spastic CP.
2. Crouch gait.
3. Deterioration in walking suggested by a reduction in speed or in walking distance or increased knee flexion in stance phase in the past year and/or pain, especially patellar pain and/or foot pain.

**Exclusion criteria**

The following were the exclusion criteria:

1. Botulinum toxin A injections within the preceding 6 months.
2. Muscle surgery within the preceding 12 months.
3. Noncommunicable patients.
4. Patients not attending regular follow-up visits.

All patients gave an informed consent, and the study protocol was approved by the Institutional Review Board of Ain Shams University.

Of the 20 patients, two patients were lost to follow-up, so the total number of patients who completed the study was 18 (34 limbs).

**Preoperative evaluation:** patients were evaluated for the following:

1. History taking, which emphasized on, but was not limited to, the following points: perinatal history, developmental history, any recent deterioration of patient activities and anterior knee pain, previous physiotherapy, and previous interventions.

2. Clinical examination: standard couch examination of each patient was done; goniometric measurements of joint ROM and deformities were done for the hip, knee, and ankle joints bilaterally; muscle power of the lower limb muscles was assessed on a five-grade scale by manual muscle testing; and observational gait analysis. Evaluate expanded and revised gross motor function classification system (GMFCS E and R) for children and youth with CP [8].

3. The functional mobility scale (FMS): this is a tool for the assessment of patient mobility. FMS was measured by asking each patient or care giver about the level of mobility. FMS uses three distances (5, 50, and 500 m), which represent typical distances walked by children at home, at school, and in the community. For each distance, a rating of 1–6 was assigned depending on the amount of assistance required for mobility (6 being the highest ability) [9].

4. Instrumented three-dimensional gait analysis: it was done for 15 cases preoperatively; of them, nine patients did postoperative gait analysis as well. Kinematics and dynamic electromyography assessments were done in the same laboratory, and it is done to formulate a surgical plan for each patient individually [10].

**Rehabilitation program**

Rehabilitation of children with CP after SEMLS was tailored according to each patient condition. We followed the following rehabilitation program [7,11].

**Preoperative rehabilitation**

It included regular ROM exercises, muscle strengthening exercises (including quadriceps, hamstrings, hip abductors, extensors, and flexors, ankle dorsiflexors, and evertors), muscle stretching to spastic muscles (hamstrings, gastrocnemius, and adductors), gait training, balance, and core exercises. Description of postoperative rehabilitation plan for parents and children is as follows:

**Postoperative rehabilitation**

*From day of surgery to 6 weeks postoperatively*

In the operated limb (which was in cast): Assisted active to active ROM exercises for unfixed joints (e.g. hips, toes) as tolerated was recommended along with strengthening of the muscles acting on unrestricted joints, from isometric progressed to isotonic exercises. Best position in bed for hips, knees, and ankles; elevation for edema control; trunk exercises; and assisted transfer education were also recommended.
Non-weight-bearing in bony surgery and weight bearing as tolerated in the case of soft tissue surgery only were initiated.

**From 6 to 12 weeks postoperatively**
This period was very important for regaining ROM and muscle strength. ROM exercises were started in previously restricted joints. Starting of isometric strengthening exercises in muscles acting on previously restricted joints progressed to isotonic and resistance exercises.

Use of heating modalities on stiff joints was common to decrease pain and improve ROM (e.g. paraffin wax or infrared radiation) with caution to avoid burns to the child.

Electric neuromuscular stimulation was added in cases with muscle recession or transfer (e.g. rectus femoris recession and tibialis anterior transfer).

Stretching exercises were started to maintain muscle length and avoid contractures and deformities of the hip, knee, and ankle flexors and adductors according to each case condition and lengthening interventions. Partial weight bearing was started with the use of orthotic devices and walker and or parallel bar for gait training.

Instructions for use of orthotic devices according to each case condition were as follows: mostly knee ankle foot orthosis was described for night positioning, ankle foot orthosis, or ground reaction ankle foot orthosis for ambulation (in case of quadriceps muscle weakness or lag).

Session frequency: five times per week for 1–2 h. Home program of simple exercises and positioning was described for adolescent children as well as parents.

**From 3 to 6 months**
Continuation of the orthotic device was done. Progressive ROM, strengthening, and stretching exercises were recommended, along with assisted balance exercises (static to semidynamic balance), and increased ambulation distance.

**From 6 to 9 months**
Continuation of the previous items, along with continuation of day use of orthotic devices was recommended. Moreover, return to preoperative level of walking and community participation was suggested.

**From 9 to 12 months**
This period led to progression to better gait, independence, and dynamic activity.

The frequency of sessions was reduced for most children and was replaced with recreational activities, including family walks, bicycle riding, and sports participation.

**Postoperative evaluation**
The patients were reviewed postoperatively at regular follow-up intervals: 6 and 12 weeks and then 3 monthly during the first year. They were evaluated by the following: standardized physical examination, observational gait analysis, the FMS, and instrumented gait analysis, which were assessed after 1 year. Patients with osteotomies were followed up by serial radiograph till complete healing.

**Statistical analysis**
All parameters were measured preoperatively and at 1-year postoperatively. The paired Wilcoxon signed-rank test was used to compare the preoperative and postoperative physical examination findings, walking speed, and FMS. The values were given as the median and the interquartile range. The significance level was defined by the probability value: $P$ value less than or equal to 0.05 was considered significant; $P$ value less than 0.01 was considered highly significant; and $P$ value more than 0.05 was considered nonsignificant.

**Results**
Ten patients were men (20 limbs, 58.82%) and eight were women (14 limbs, 41.18%). Age ranged from 5.5 to 19 years, with a mean age of 12 years.

The 18 patients were classified according to the expanded and revised GMFCS E and R for children and youth with CP [11]. Five (27.8%) were GMFCS II, 10 (55.5%) were GMFCS III, and three (16.7%) were GMFCS IV. All patients had had bilateral spastic diplegic CP. Two of them have had an inborn error of metabolism, namely (well controlled), maple syrup urine disease. Eleven (61%) patients had previous interventions, either surgery or Botox injection (>1 year and 6 months before index procedure, respectively), especially of the calf muscles.

Preoperative and 1-year postoperative values for six physical examination parameters are described in Table 1. Data from both sides were added. Most of the values at 1-year postoperatively were highly significantly different from the preoperative values ($P<0.01$).
Values of FMS at 5, 50, and 500 m are described in Tables 2 and 3. FMS at 5, 50, and 500 m improved in 10 (55.6%) cases, 13 (72.2%) cases, and 11 (61.1%) cases, respectively.

Preoperative and 1-year postoperative values of three gait laboratory parameters, namely, stride length, crouch angle at initial stance, and peak knee flexion in mid-swing, are represented in Table 4.

Example of improvement of cases is represented by a case of a male patient, 13 years old, with GMFCS III. He had a history of obstructed labor and delayed developmental milestones. Botox injections to hamstring and gastrosoleus four times were followed by right hamstring lengthening 2 years before his index surgery. He was subjected to bilateral femoral supracondylar extension derotation osteotomy, bilateral patellar tendon advancement, bilateral gastrocnemius recession, and right supramalleolar derotation osteotomy, and correction of both feet deformities were done by a double team working simultaneously. Rehabilitation program started at day 5 postoperatively and continues till 1 year.

At 1-year postoperatively, the patient improved in terms of clinical parameters, especially femoral anteversion, fixed knee flexion deformity, extension lag, and foot deformity (Fig. 1). FMS was improved at 50 m only. There were improvements in walking speed. Postoperative gait laboratory parameters showed improvement in knee kinematics and hip rotation as compared with preoperative curves (Fig. 2).

### Table 1 Preoperative and postoperative functional mobility scale compared with the preoperative level

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Wilcoxon signed-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
</tr>
<tr>
<td>Hip abduction</td>
<td></td>
<td></td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Left</td>
</tr>
<tr>
<td>Femoral anteverision</td>
<td>22.5</td>
<td>10–35</td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>15–40</td>
<td>Left</td>
</tr>
<tr>
<td>Knee fixed flexion deformity</td>
<td>5</td>
<td>0–15</td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td>8.5</td>
<td>5–15</td>
<td>Left</td>
</tr>
<tr>
<td>Pop angle</td>
<td>50</td>
<td>40–60</td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td>57.5</td>
<td>40–60</td>
<td>Left</td>
</tr>
<tr>
<td>Extension lag</td>
<td>15</td>
<td>5–25</td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td>17.5</td>
<td>7–30</td>
<td>Left</td>
</tr>
<tr>
<td>Tibial rotation</td>
<td>15</td>
<td>15–25</td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td>17.5</td>
<td>15–30</td>
<td>Left</td>
</tr>
</tbody>
</table>

HS, highly significant; IQR, interquartile range; S, significant.

### Table 2 Follow-up assessment of postoperative functional mobility scale compared with the preoperative level

<table>
<thead>
<tr>
<th>Parameter</th>
<th>The same</th>
<th>Decreased</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMS 5</td>
<td>8 (44.4)</td>
<td>0</td>
<td>10 (55.6)</td>
</tr>
<tr>
<td>FMS 50</td>
<td>4 (22.2)</td>
<td>1 (5.6)</td>
<td>13 (72.2)</td>
</tr>
<tr>
<td>FMS 500</td>
<td>7 (38.9)</td>
<td>0</td>
<td>11 (61.1)</td>
</tr>
</tbody>
</table>

FMS, functional mobility scale.

### Table 3 Follow-up assessment values of functional mobility scale

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Wilcoxon signed-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
</tr>
<tr>
<td>FMS 5</td>
<td>4</td>
<td>2–6</td>
<td>5</td>
</tr>
<tr>
<td>FMS 50</td>
<td>3.5</td>
<td>2–5</td>
<td>4.5</td>
</tr>
<tr>
<td>FMS 500</td>
<td>2.5</td>
<td>1–5</td>
<td>3.5</td>
</tr>
</tbody>
</table>

FMS, functional mobility scale; HS, highly significant; IQR, interquartile range.

### Table 4 Preoperative and postoperative values of three IGA parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Wilcoxon signed-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
</tr>
<tr>
<td>Stride length</td>
<td>0.578</td>
<td>0.394–0.836</td>
<td>0.443</td>
</tr>
<tr>
<td>Crouch angle</td>
<td></td>
<td></td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Left</td>
</tr>
<tr>
<td>Peak knee flexion</td>
<td></td>
<td></td>
<td>Right</td>
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<tr>
<td></td>
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<td>Left</td>
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</tbody>
</table>

IQR, interquartile range. IGA, Instrumental Gait Analysis.

### Discussion

There is limited information available about post-SEMLS rehabilitation [12]. Evidence was found for large improvements in gait with more equivocal evidence for changes in gross motor function [12]. Orthopedic surgery results in weakness, loss of independence, and decreased gross motor function,
which makes rehabilitation after SEMLS challenging [7].

No previous comparative studies have been conducted to compare different rehabilitation protocols. Ten of our patients were men and eight were women. Their age ranged from 5.5 to 19 years, with a mean age of 12 years. Most children showed a plateau in gait and gross motor function, diminishing response to botulinum toxin injections, and the progression of fixed contractures between the age of 5 and 8 years, and this is the time when serious planning for SEMLS should start [7].

A total of 146 procedures were done to the patients: 92 soft tissue procedures and 54 bony procedures. Apart from the two missed cases, 18 patients were highly compliant to rehabilitation sessions and follow-up visits. The clinical parameters of our patients showed a highly significant improvement in hip abduction, femoral anteversion, fixed flexion deformity of the left knee, popliteal angle, and extension lag of knees, whereas there is significant improvement of tibial rotation and right knee fixed flexion deformity.

In our study, we observed that the pattern of change differed according to the functional level preoperatively. Children with GMFCS II walked without assistive devices at household distances and therefore had improved statistically significantly at greater distances. Children with GMFCS levels III and IV had improved more at short distances and the greatest change was at 5 m. FMS of 5, 50, 500 m improved in 10 (55.6%) cases, 13 (72.2%) cases, and 11 (61.1%) cases, respectively. Our patients reached the preoperative level at 6 months postoperatively. This
agrees with other studies. The world’s first randomized controlled trial of SEMLS was published by the team at the Royal Children’s Hospital in Melbourne. This randomized clinical trial reported a 57% improvement in gait according to the Gillette Gait Index and a 4.9% improvement in gross motor function according to the GMFM-66 [13].

Terjesen et al. [14] studied gait improvements in 34 ambulatory children with spastic diplegia after multilevel surgery. They evaluated the functional level using the FMS and found the same results, as compared with our study, at 1 year. Moreover, 5-year postoperatively, children at GMFCS level III showed improvements at FMS 500 m [14].

Harvey and colleagues examined the ability of the FMS to detect changes in children with CP undergoing SEMLS. Their study was a retrospective one and comprised 66 children. For each FMS distance (5, 50, and 500 m), odds ratios showed a significant deterioration in mobility at 3 and 6 months postoperatively. Mobility then improved to baseline levels by 12 months and improved further by 24 months postoperatively [8].

Regarding the complications in this series, there is a need for additional surgery in four (22.2%) patients. Even if SEMLS is aiming at correcting all existing deviations in gait, additional surgery is sometimes necessary. Kay et al. [15] found a need for such surgery already at the 1-year follow-up. Preoperative and 1-year postoperative values of three gait laboratory parameters, namely, stride length, crouch angle at initial stance, and peak knee flexion in mid-swing, showed improvement but did not reach statistical significance, which may be owing to the small sample size, as preoperative and postoperative instrumented three-dimensional gait analyses were done for only nine cases. It may be also owing to the short follow-up period. Dequeker et al. [16] found a significant increase in the pediatric evaluation of disability, the mobility questionnaire, and FMS at 6 months and 1 year, which agrees with our results. Dreher et al. [17] found that ambulatory children aged 10 years and 7 months with GMFCS levels I, II, and III undergoing multilevel surgery showed a decrease (improvement) in preoperative gait profile score from 16.3° to 11.3° at short-term follow-up, and improvement of 5° at long-term follow-up. A large systematic review [18] on hip dislocation in children with CP has clearly revealed these short comings of retrospective studies, thus the body of evidence on the treatment outcomes of retrospective studies is considerably more limited than for prospective studies.

Our study was prospective, and rehabilitation is the main scope, which is present in few studies and is considered a strength point. We consider the relatively small sample size as important limitations. The generalizability of the findings would also have been improved with a larger study sample and a longer follow-up period.

Conclusion

At 1-year postoperatively, there were significant improvements in all clinical parameters and FMS. These measures reflect clinical improvement of patients and their functional mobility, denoting the essential role of rehabilitation in these patients.

Acknowledgements

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Nil.

Conflicts of interest

There are no conflicts of interest.

References


Premature ovarian failure in systemic lupus erythematosus patients: is it related to cyclophosphamide treatment?

Rasha M. Ghaleb, Khaled A. Fahmy

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune systemic disease that mainly affects women during the childbearing period. Cyclophosphamide (CYC) is the drug of choice for severe SLE manifestations. However, many side effects had been reported. Premature ovarian failure (POF) is one of the serious complications that can occur in SLE patients.

Aim

The aim was to evaluate the prevalence of POF in female patients with SLE and whether it is related to CYC treatment or not.

Patients and methods

One hundred women with SLE satisfying the updated revised criteria for the classification of SLE were studied. The patients were allocated into two groups: CYC-treated group (n=55) and non-CYC-treated group (n=45). Patients were interviewed and demographic characteristics, clinical and serologic profiles, and menstrual histories were recorded. Disease activity was measured by the SLE disease activity index. Serum anti-Müllerian hormone was measured as a marker for ovarian reserve assessment in the two study groups.

Results

Ovarian failure occurred in 15 (27.3%) patients out of the 55 SLE patients treated with CYC. The cumulative CYC dose was significantly higher in patients with ovarian failure than in those without this condition (11.7 vs. 9.5 g; P=0.001). The cumulative dose of CYC and the older age at initiation were found to be associated more with POF.

Conclusion

In our population of female SLE patients, CYC-induced ovarian failure is a significant problem occurring in 27.3% of SLE patients receiving CYC. So, for SLE patients in whom the use of CYC is mandatory, a lower dosage and a shorter course of this agent should be considered. Co-treatment with gonadotropin-releasing hormone agonists might persevere the future fertility and ovarian function in young women. Ovarian banking before administration of CYC could be a possible solution in certain cases.

Keywords:
cyclophosphamide, intravenous cyclophosphamide, premature ovarian failure, systemic lupus erythematosus

Introduction

Autoimmune diseases may selectively affect women in their reproductive years [1]. Systemic lupus erythematosus (SLE) is an autoimmune disease that affects most women of reproductive age [2]. It is characterized by deficiency of body’s immune response that leads to the production of autoantibodies and failure of immune complex clearance [3]. Management of SLE is challenging due to the heterogeneous presentation and clinical manifestations of the disease [4].

Cyclophosphamide (CYC) is an alkylating agent that acts by transferring alkyl groups to biologically important cellular constituents [5]. CYC is a potent cytotoxic agent that has been reported to have important effects on the immune system, such as modulation of T-cell activation and inhibition of immunoglobulin production from B cells [6]. It remains the ‘gold standard’ treatment for severe organ-threatening SLE, especially renal and central nervous system lupus [7]. However, many side effects of long-term exposure to this drug had been reported including infection, bone marrow damage, malignancy, hemorrhagic cystitis, and premature ovarian failure (POF) [8].
POF is an ovarian defect characterized by the premature depletion of ovarian follicles before the age of 40 years [9]. POF is not merely an early menopause. Up to 50% of the patients with POF will have intermittent and unpredictable ovarian function which may persist for some years [10]. Moreover, POF is not only a problem of fertility, but also causes in the acceleration of arteriosclerosis and osteoporosis [11].

This study was therefore conducted to evaluate the prevalence of POF in female patients with SLE and whether it is related to CYC treatment or not.

**Patients and methods**

**Patients**

This was a cross-sectional study, conducted between May 2011 and April 2012. It included 100 female patients with SLE aged from 18 to 39 years; disease duration ranged from 1.5 to 12 years. The patients were diagnosed according to the American College of Rheumatology criteria [12]. All patients were either outpatients or inpatients of Rheumatology and Rehabilitation Department of El-Minia University Hospital, Egypt. The study was carried out with the approval of local ethics committee and in accordance with the national law and the Helsinki Declaration of 1975. Informed consent was obtained from all patients.

**Exclusion criteria**

Female patients who did not satisfy the American College of Rheumatology criteria, patients younger than 18 years or above 40 years, those with a family history of POF, SLE women with renal failure or on dialysis, patients with primary or secondary amenorrhea due to a known cause such as previous oophorectomy, pelvic irradiation, or hysterectomy. Current users of hormonal therapy and those in whom menopause had occurred before CYC treatment were also excluded from the study.

**Data collection**

The studied patients were allocated into two groups: CYC-treated group (n=55) and non-CYC-treated group (n=45). The following information was obtained from all patients: demographic data, age at onset of SLE, disease duration, autoantibody profile at presentation and clinical features during the course of the disease. For those who received CYC, age at the initiation of CYC and total cumulative doses received were calculated and recorded.

**Systemic lupus erythematosus activity**

Current SLE disease activity was measured using the SLE disease activity index (SLEDAI) [13]. The SLEDAI is scored on 24 items observed during the preceding 10 days. Among the various instruments developed for assessing lupus activity, the SLEDAI was chosen for its validity and relatively low cost to complete [14].

**Treatment regimens of cyclophosphamide**

The CYC studied group who received the standard induction regimen, which was monthly intravenous cyclophosphamide (IV-CYC) at 750 mg/m² body surface area for 6 months before being included in the study, followed by a maintenance regimen of quarterly infusions for 2 years. The duration of the IV-CYC courses was adjusted according to clinical response and adverse effects. The dosage of CYC was also adjusted according to white blood cell count and the regimen was modified when there is leukopenia, infection, gastrointestinal tract intolerance, or when there was noncompliance with the treatment regimen.

**Interventions**

All SLE patients included in the study were subjected to the following.

**Routine investigations**

Simple urinalysis, 24-h urinary albumin, complete blood picture, first hour erythrocyte sedimentation rate (Westergren), serum aspartate aminotransferase and alanine aminotransferase, serum creatinine and blood urea, antinuclear antibody (ANA) by immunofluorescence technique, anti-ds DNA by enzyme-linked immunosorbent assay (ELISA), and anticardiolipin antibodies by ELISA were done for all patients.

**Assessment of ovarian function**

1. Detailed menstrual history.
2. Anti-Müllerian hormone assay (AMH).

**Detailed menstrual history of participants included**

Age of menarche, duration of menses, cycle length, and reliable last menstrual period (premorbid, preinduction, during induction, and during maintenance of CYC therapy). In the current study, those who had lack of menses for more than 3 months are categorized as having secondary amenorrhea.

**Details of anti-Müllerian hormone assay**

We used the Human Müllerian Inhibiting Substance/AMH, MIS/AMH ELISA Kit (MIS/AMH Elisa® Immnotech, Bechman-Coulter, California, USA), catalog no: E0228hElaabTM. A calculated cutoff level of less than or equal to 1.26 ng/ml AMH was the laboratory diagnosis of women developing ovarian failure [15].
Statistical analysis
Data were analyzed by the Statistical Package for the Social Sciences (SPSS, version 21; SPSS Inc., Chicago, Illinois, USA). Differences in frequencies were analyzed by $\chi^2$-test and Fisher’s exact test as appropriate. Student’s $t$-test was used to compare parametric data while the $\chi^2$-test was used when the data were nonparametric. Associations between interval, ordinal, and dichotomous variables were tested by Pearson’s product moment correlation coefficients ($r$). Two-tailed tests were used throughout, with statistical significance set at the conventional 95% level.

Results
Demographic data and clinical features
The mean age of SLE patients ($n=100$) was 31.2±5.7 (range: 18–39 years); the mean age of onset was 25.7±4.7 (range: 16.5–34.5 years); and the mean duration of illness was 5.5±2.4 (range: 1.5–12 years). None of the studied patients were smokers or alcohol drinkers.

At the time of the study, 55 patients were treated with IV-CYC. High-dose corticosteroid (prednisolone 1 mg/kg/day) was administered concomitantly in all CYC-treated patients and the dose was gradually tapered to a maintenance dose of 5–10 mg/day after 8–12 weeks. Antimalarial treatment was also administered to this entire group of patients. On the other group of SLE patients who never received CYC ($n=45$), antimalarial treatment was in use by 41 patients, steroids were in use by 19 patients, azathioprine was in use by 11 patients while mycophenolate mofetil was used in only five cases. The main indications of CYC therapy is summarized in Table 1.

Comparison between cyclophosphamide-treated patients and noncyclophosphamide-treated patients
SLE patients who were on CYC treatment were significantly younger, had an earlier disease onset, a lower disease activity index ($P<0.001$) than SLE patients who had never been treated with CYC, but the difference was not statistically different between the two groups in disease duration, number of swollen joints, or articular index (Table 2).

Moreover, no significant differences were noted in various clinical manifestations of SLE in both groups, except that the CYC-treated group had a statistically higher frequency of renal affection (Table 3).

By comparing the different laboratory parameters between the two groups of SLE patient; only titer of anti-dsDNA was statistically higher in that group treated with CYC than the other group of SLE patients, while other laboratory parameters did not statistically differ. Meanwhile, the level of AMH was significantly lower in the CYC-treated group when compared with the other group who did not receive the CYC therapy (Table 4).

Cyclophosphamide-induced premature ovarian failure
In SLE patients receiving CYC therapy, 15 (27.3%) patients had prolonged amenorrhea with documented ovarian failure, while none of the patients who did not receive CYC therapy had developed this complication.

By comparing the ovarian failure group ($n=15$) and the menstruating group ($n=40$) within the CYC-treated SLE patients ($n=55$), we found that the SLE patients who developed POF were significantly older, had a later disease onset, a more cumulative dose of CYC than the menstruating SLE patients group (Table 5).

In CYC-treated SLE patients, the presence of POF was significantly positively correlated with age of the SLE patient, activity of SLE, age at initiation of CYC treatment ($P<0.05$), and was highly correlated with the

<table>
<thead>
<tr>
<th>Table 1 Main indications of cyclophosphamide in systemic lupus erythematosus treated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE patients ($n=55$)</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Lupus nephritis</td>
</tr>
<tr>
<td>CNS cerebritis</td>
</tr>
<tr>
<td>Both lupus nephritis and cerebritis</td>
</tr>
<tr>
<td>Lupus vasculitis</td>
</tr>
</tbody>
</table>

CNS, central nervous system.

<table>
<thead>
<tr>
<th>Table 2 Comparison between demographic features and systemic lupus erythematosus disease-related parameters in cyclophosphamide-treated systemic lupus erythematosus patients versus noncyclophosphamide-treated group</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYC-treated group ($n=55$) (mean±SD)</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Age at onset (years)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
</tr>
<tr>
<td>Articular index</td>
</tr>
<tr>
<td>Number of swollen joints</td>
</tr>
<tr>
<td>SLEDAI</td>
</tr>
</tbody>
</table>

CYC, cyclophosphamide; SLEDAI, systemic lupus erythematosus disease activity index. *$P<0.05$, significant difference. **$P<0.01$, significant difference.
The goal of this study was to evaluate the prevalence of POF in female patients with SLE and whether it is related to CYC treatment or not.
Our study included 100 Egyptian SLE patients satisfying the updated revised criteria for the classification of SLE [12]. Diagnosis of ovarian failure was based on menstrual history and AMH assay.

In the present study, POF was developed in 15 (27.3%) of the SLE patients receiving CYC therapy. In accordance with our results, there was a prevalence of 26% in a study of 70 premenopausal female patients who were treated with both oral and intravenous form of CYC [26]. Another one showed a prevalence of 24% in a study of 17 women with lupus nephritis who were treated with IV-CYC [22].

A higher incidence had been reported by other studies. In an earlier investigation by Warne et al. [20], who studied 20 female patients who had received oral CYC for an average of 19 months for the treatment of glomerulonephritis, 11 (55%) patients out of the 20 developed amenorrhea, which persisted during a follow-up period of 5–31 months after discontinuation of CYC. Another study by McDermott and Powell [27] had reported that the incidence of ovarian failure in the premenopausal CYC-treated group was 54%.

On the contrary, D’Cruz et al. [28] reported that none of his patients had developed any menstrual abnormalities with the intravenous CYC regimen. This was probably because the majority of his patients received no more than 2.5 g of CYC. In that study, weekly intravenous pulses of 500 mg was used for 3–5 weeks to achieve partial or complete remission for the treatment of lupus nephritis, followed by oral CYC 2 mg/kg/day or azathioprine 2 mg/kg/day. The authors commented that the risk of ovarian failure was markedly reduced with the use of this shorter regimen of CYC.

The main explanation of this variation of the prevalence rates might be due to the fact that most of the studies mentioned before were retrospective studies in which incomplete or unclear records may confound the results of this type of studies. Another important factor could be related to the discrepancy in the treatment protocols, differences in the route of administration of CYC whether oral form or intravenous form, and hence, the cumulative doses of CYC administered will differ.

Differences in the age of the patients recruited may play a role in this variation as the reserve of ovarian follicles appears to be an important key factor in the risk for ovarian failure related to CYC treatment [26]. In our study, POF was increased with increasing the age of the patients. Most studies [19,27] have consistently demonstrated a trend of increasing risk for ovarian failure with increasing age. Actually and under normal circumstances, the number of ovarian follicles decreases steadily with age until the last decade before menopause, when the number falls even more dramatically [29]. This explains our results that why patients who are younger at the start of CYC therapy are more resistant to CYC-induced ovarian damage.

## Table 5 Comparison between ovarian failure group and menstruating group within cyclophosphamide-treated systemic lupus erythematosus patients (n=55)

<table>
<thead>
<tr>
<th></th>
<th>Ovarian failure patients (n=15) (mean±SD)</th>
<th>Menstruating patients (n=40) (mean±SD)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.3±3.6</td>
<td>28.3±5.6</td>
<td>4.4 0.01**</td>
</tr>
<tr>
<td>Age at onset of SLE</td>
<td>26.1±3.5</td>
<td>23.5±4.6</td>
<td>3.4 0.001**</td>
</tr>
<tr>
<td>Cumulative dose of CYC</td>
<td>29.2±3.5</td>
<td>25.7±4.7</td>
<td>3.9 0.001**</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>17.7±8.5</td>
<td>10.4±5.9</td>
<td>4.5 0.001**</td>
</tr>
<tr>
<td>AMH levels (ng/ml)</td>
<td>0.6±0.3</td>
<td>1.8±0.3</td>
<td>1.2 0.001**</td>
</tr>
</tbody>
</table>

AMH, anti-Müllerian hormone; CYC, cyclophosphamide; SLEDAI, systemic lupus erythematosus disease activity index. *P<0.05, significant difference. **P<0.01, significant difference.

## Table 6 Correlation between premature ovarian failure and different systemic lupus erythematosus disease manifestations

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.33</td>
<td>0.02*</td>
</tr>
<tr>
<td>Age at onset</td>
<td>0.25</td>
<td>0.07</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>0.24</td>
<td>0.09</td>
</tr>
<tr>
<td>Age at start of CYC</td>
<td>0.32</td>
<td>0.02*</td>
</tr>
<tr>
<td>Cumulative dose of CYC</td>
<td>0.37</td>
<td>0.006**</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>0.31</td>
<td>0.02*</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>0.22</td>
<td>0.12</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>0.20</td>
<td>0.15</td>
</tr>
<tr>
<td>DNA</td>
<td>0.15</td>
<td>0.29</td>
</tr>
<tr>
<td>Anticardiolipin</td>
<td>0.29</td>
<td>0.03*</td>
</tr>
<tr>
<td>AMH</td>
<td>-0.90</td>
<td>0.001**</td>
</tr>
</tbody>
</table>

AMH, anti-Müllerian hormone; CYC, cyclophosphamide; SLEDAI, systemic lupus erythematosus disease activity index. *P<0.05, significant difference. **P<0.01, significant difference.
In the present study, no one of our SLE patients who were never treated with CYC had POF. This could be explained by that the occurrence of ovarian failure in the CYC-treated group was due to the cytotoxic effect of CYC rather than due to the disease itself. Factors other than CYC which may influence the development of ovarian failure were also studied as none of our patients were smokers or alcohol drinkers, no association was found between POF and azathioprine or mycophenolate mofetil usage which is in agreement with the study by Silva et al. [30].

In the present study, POF was increased with a higher cumulative dose of CYC. Several studies [31–33] in the literature strongly support an association between the early occurrence of ovarian failure and the cumulative dose of CYC. Medeiros et al. [33] found his SLE patients treated with a cumulative CYC dose greater than 10 g had a 3.2 times higher risk of developing ovarian insufficiency than patients receiving a cumulative dose lower than 10 g. [33]. Mok et al. [26] found that the mean cumulative CYC dose was higher (28 g) in the group with ovarian failure, while it was 15 gm in the group without ovarian failure. Most of the studies mentioned before used serum follicle-stimulating hormone (FSH) as a marker of ovarian function as it has long been recognized and remains in very widespread clinical use. However, significant problems may arise with FSH measurement like marked intercycle variation and the need for blood sampling in the early follicular phase of the menstrual cycle [34]. On the contrary, AMH is a product of the granulosa cells of small growing follicles and its expression increases as soon as the follicle starts to grow and importantly falls to low levels at the early antral stage of development [35,36]. This means that serum AMH is much more stable over the menstrual cycle than other ovarian follicle hormones (inhibins A and B, estradiol) and FSH [37,38]; thus for practical purposes, blood sampling can be undertaken on any day of the cycle [34].

However, our study has some limitations. The first limitation of the study come from the point that some of the data related to the menstrual history like age at menarche, menstrual regularity, and duration of amenorrhea was relatively inaccurate as they relied upon participant recall. However, amenorrhea was not evaluated by only history as we depend mainly on serum AMH as a sensitive marker of POF. The second limitation was involved with some problems related to interpretation of AMH hormone levels as a marker of ovarian failure. This is because the test has not been in routine use for many years; the levels considered to be ‘normal’ are not yet clarified and agreed on by the experts. Longer follow-up is needed to reveal putative differences.

**Conclusion**

In conclusion, this study had characterized ovarian function in female patients with SLE assigned for CYC therapy using AMH as a sensitive marker. Our results showed that ovarian failure was a significant problem in this CYC-treated patient group, occurring in about 27.3% of the cases. In case of absence of CYC treatment, the prevalence of POF in SLE patients is consistent with the general population reports.

We recommend that for older patients who do not complete their families, in whom the use of CYC is warranted, a shorter course and lower dosage could be considered. Also, it is recommended for care givers for SLE patients to arrange for AMH assay before initiating CYC therapy as a better step toward counseling women at risk of ovarian failure. Modifying treatment protocols by suggesting azathioprine or mycophenolate mofetil as a cyclophosphamide CYC-sparing agent for long-term therapy. To preserve ovarian function, co-treatment with gonadotropin-releasing hormone analog may persevere the future fertility and ovarian function in women with severe lupus. Ovarian banking before administration of CYC should be considered in selected patients.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**


Neuromuscular ultrasound in ulnar neuropathy at the elbow: correlation with electrodiagnostic studies
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Introduction
Ulnar nerve entrapment is the second most common entrapment neuropathy in the upper limb after carpal tunnel syndrome, and, if left untreated, it may lead to significant functional impairment and disability.

Objective
The aim of this study was to perform clinical, electrodiagnostic (EDX), and neuromuscular ultrasound assessment for patients with ulnar neuropathy at the elbow, to determine the possible roles of neuromuscular ultrasound in the localization of the neuropathy, in the detection of its possible etiologies and in the determination of its severity.

Patients and methods
A sample of 15 (22 elbows) patients was recruited and subjected to full medical history, neurological assessment, EDX studies, and neuromuscular ultrasound examination. Ten (20 elbows) age-matched and sex-matched healthy volunteers were also recruited and served as a control group.

Results
This study revealed significantly enlarged ulnar nerve cross-sectional area (CSA) at the ulnar groove and below the elbow and supracondylar sites in patients compared with the control group. receiver-operating characteristic curve analysis revealed high diagnostic accuracy of the absolute CSA at the ulnar groove, and below the elbow and supracondylar sites, with an area under the curve of 0.8, 0.8, and 0.9, respectively, and the cutoff values were >9, >8, and >8, respectively. The area under the curve for the ‘maximum CSA/midforearm CSA ratio’ was 0.9, with a cutoff value of more than 1.3.

Conclusion
Our study data suggest that neuromuscular ultrasound (NMUS) examination may play a potentially important role in the assessment of ulnar neuropathy at the elbow. It can localize the lesion and disease severity, and it can differentiate between patients and controls, given its high diagnostic ability. Abnormalities in ultrasonographic features of ulnar nerve entrapment with regard to CSA and ratio between ‘maximum CSA and midforearm CSA’ at the elbow was correlated with EDX findings.

Keywords:
cubital tunnel syndrome, electrodiagnosis, nerve cross-sectional area, neuromuscular ultrasound, ulnar neuropathy at the elbow

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proven itself as a valuable complementary tool to EDX studies. While EDX studies assess the functional aspect of the nerve, neuromuscular ultrasound evaluates the anatomical aspect. Nowadays, ultrasound is able to identify successfully almost all main nerve trunks running in the limbs [5].

Several studies have been performed to evaluate the ultrasound findings in ulnar neuropathy. These studies have shown that focal enlargement of the ulnar nerve at the elbow is a relevant component of ulnar neuropathy and thus can be helpful as an adjunct to EDX studies in detecting patients with cubital tunnel syndrome [6].

Ultrasonography of the elbow offers a number of advantages over other imaging tools such as MRI, including being less time consuming, having no radiation, facilitates easy comparison with the other side, has a better cost-effectiveness ratio, superior spatial resolution and dynamic capability [7].

Most of the published studies focused on the ultrasonographic appearance of the ulnar nerve in ulnar neuropathy at the elbow but few addressed its correlation with EDX studies.

**Objective**

The objectives of this study were to determine the possible roles of neuromuscular ultrasound in localizing the neuropathy and in detecting its possible etiologies, and to correlate the sonographic findings with the EDX findings.

**Patients and methods**

This study was carried out on 15 (22 elbows) patients who presented to the outpatient clinic or to the Electrodiagnostic Unit of the Physical Medicine, Rheumatology and Rehabilitation Department at Ain Shams University Hospitals. Ten (20 elbows) apparently healthy individuals of matched age and sex were recruited from the same hospital and served as a control group to compare neuromuscular ultrasound findings in patients versus controls.

Inclusion criteria: patients with characteristic symptoms and signs of ulnar neuropathy at the elbow were included.

The clinical diagnosis of cubital tunnel syndrome was made if the patient complained of pain, numbness and or tingling in the ring and little fingers, especially if it increased with elbow flexion and/or weakness of the ulnar-innervated muscles, with or without positive Tinel’s sign.

All patients were subjected to the following:

1. Full medical history with special emphasis on the onset, course, and duration of the patient’s symptoms, distribution of paresthesia, tingling, and numbness, distribution of weakness if any, and any functional limitations during activities of daily living.
2. Clinical examination, which included general examination and full neurological and musculoskeletal examination.
3. Plain radiographs of the elbow joint to assess for any deformities, degenerative changes, or soft-tissue calcifications.
4. Nerve conduction studies:

   a. Motor nerve conduction study of the ulnar nerve, with recording from the abductor digiti minimi and stimulation at the wrist, below the elbow (3–4 cm distal to the medial epicondyle) and above the elbow (10 cm from the below-elbow stimulation site). The study was repeated with recording from the first dorsal interosseus, performing inching technique and mixed and sensory conduction studies if EDX demonstrated axonal features alone, with no evidence of focal demyelination at the elbow.

   b. Sensory conduction study of the ulnar nerve with recording from the ring and little fingers, and stimulation at the wrist, below the elbow and above the elbow.

   c. Motor and sensory conduction studies of the median nerve, and sensory conduction study of the radial nerve, to exclude more widespread polyneuropathies and thoracic outlet syndrome.

   d. F-wave study of the ulnar and median nerves to assess the proximal roots.

The patient was diagnosed as having EDX-proven ulnar neuropathy at the elbow if one of the following patterns was found:

Pattern 1: Ulnar neuropathy at the elbow if one of the following patterns was found:

a. Low ulnar sensory nerve action potential (<15 μv at the below-elbow or 14 μv above-elbow sites).

b. Normal or low-amplitude ulnar compound muscle action potential (CMAP) [<4 mV with normal or slightly prolonged distal latency (>3.4 ms)].
(c) Unequivocal evidence of demyelination at the elbow (conduction block and/or slowing > 10–11 m/s across the elbow compared with the forearm segment, in the flexed elbow position).

Pattern 2: Ulnar neuropathy at the elbow with pure demyelinating features:
(a) Normal distal ulnar sensory nerve action potential and CMAP amplitudes and latencies.
(b) Unequivocal evidence of demyelination at the elbow (conduction block and/or slowing > 10–11 m/s across the elbow compared with the forearm segment, in the flexed elbow position).

(5) Neuromuscular ultrasound of the ulnar nerve (was performed for all patients and controls).

The study was performed using LOGIQ P5 ultrasound system (General Electric Company, New York, New York, USA) and 13 MHz linear array transducer. The ulnar nerve was imaged in two views: axial (Fig. 1) and longitudinal (Fig. 2). In the axial view, the nerve was traced from the wrist (level of Guyon's canal) to the midarm level and was assessed as regards size, echogenicity, vascularity and mobility.
Moreover, the surrounding structures were screened for any abnormalities, or anatomical variants like accessory muscles.

Nerve cross-sectional area (CSA) was measured at the site of maximal enlargement, which was at either the ulnar groove or the below elbow or supracondylar sites. The ratio between the area of maximal enlargement/midforearm CSA was calculated. The CSA was measured using the trace function by tracing the nerve just inside its hyperechoic rim. Care was taken during scanning to ensure orthogonal orientation of the probe at all times and that least pressure was exerted by the probe. Echotexture was assessed by observing and recording any change including hypoechogenicity of the nerve, loss of typical honeycomb appearance, focal enlargement of one fascicle, diffuse enlargement of all fascicles or change in the echotexture of the outer epineurium.

Mobility was assessed by placing the probe at the ulnar groove in the axial view with the elbow extended with the release of any pressure by the probe, and then the patient was asked to actively and gradually flex the elbow to observe any subluxation or dislocation of the nerve. The nerve was considered subluxated if the ulnar nerve moved anteriorly to the apex of the medial epicondyle but did not snap over the medial epicondyle, and was considered dislocated if the ulnar nerve snapped completely over the medial epicondyle during flexion with reduction to normal position in extension.

**Statistical analysis**

Statistical analysis was conducted and analyzed using statistical package for the social sciences program (SPSS) software version 20.0 (IBM SPSS statistics for windows, version 20.0 Armonk, NY: IBM corp., SPSS inc., IBM corporation). Quantitative data were expressed as mean±SD. Student’s t-test was used for comparison of two means. Paired t-test was used to determine whether the mean difference between two sets of observations was zero, and χ²-test was used for testing relationships between categorical variables.

The level of significance was taken at P value up to 0.05. Descriptive statistics were performed for quantitative data as minimum and maximum of the range as well as the mean and the SDs for quantitative parametric data, while it was performed for qualitative data as number and percentage. A receiver-operating characteristic (ROC) analysis was performed to determine the sensitivity and the specificity of the ulnar nerve diameter and the amplitude of ulnar nerve conduction studies.

Correlation studies were performed using Pearson’s correlation test (r); P value equal to or less than 0.05 was considered a statistically significant difference.

**Results**

This table shows that the ulnar nerve CSA was significantly enlarged in patients compared with controls at below-elbow [between the two heads of flexor carpi ulnaris (FCU)], ulnar groove and above-elbow (supracondylar) sites (P≤0.05; Table 1). Moreover, the ratio between maximum CSA and midforearm CSA was significantly higher in patients compared with the controls (P≤0.05; Table 1).

| Table 1 Comparison of ulnar nerve cross-sectional area between patients and control groups |
|-----------------------------------------------|------------------|------------------|-----------------|-----------------|
| Ulnar nerve cross-sectional area by ultrasound | Patients (N=22) | Control (N=10)  | t-Test          | P value         |
| Guyon’s canal (mm²)                            |                  |                  |                 |                 |
| Mean±SD                                       | 6.09±2.24        | 5.45±1.23        | 1.277           | 0.265           |
| Range                                         | 4–13             | 4–8              |                 |                 |
| Midforearm (mm²)                              |                  |                  |                 |                 |
| Mean±SD                                       | 6.64±2.59        | 5.80±1.28        | 1.701           | 0.200           |
| Range                                         | 4–14             | 4–8              |                 |                 |
| Below the elbow (between two heads of FCU) (mm²)|                  |                  |                 |                 |
| Mean±SD                                       | 8.82±2.97        | 5.95±1.43        | 15.374          | <0.001**        |
| Range                                         | 5–16             | 4–8              |                 |                 |
| Ulnar groove                                  |                  |                  |                 |                 |
| Mean±SD                                       | 12.45±5.93       | 6.50±1.47        | 19.038          | <0.001**        |
| Range                                         | 5–27             | 4–9              |                 |                 |
| Supracondylar area                            |                  |                  |                 |                 |
| Mean±SD                                       | 8.95±3.26        | 5.80±1.28        | 16.407          | <0.001**        |
| Range                                         | 4–17             | 4–8              |                 |                 |
| Ratio between maximum cross-sectional area and midforearm |                  |                  |                 |                 |
| Mean±SD                                       | 2.06±1.01        | 1.13±0.09        | 16.980          | <0.001**        |
| Range                                         | 1.07–4.25        | 1–1.25           |                 |                 |

*P >0.05 is non-significant. **P ≤0.01, highly significant. FCU, flexor carpi ulnaris.
There was a statistically significant positive correlation between ulnar nerve CSA values at both the ulnar groove and below the elbow and the distal motor latency (DML), whereas there was a statistically significant negative correlation between ulnar CSA values at below elbow, ulnar groove and supracondylar sites with below-elbow amplitude. There was a statistically significant negative correlation between ulnar CSA values at the below elbow and ulnar groove sites with each of the following EDX parameters: DML and CMAP distal amplitude and conduction velocity. There was also a highly significant negative correlation between ulnar CSA at the ulnar groove and above-elbow amplitude (\(P \leq 0.05\); Table 2).

Table 3 shows the correlation between nerve conduction parameters and ratio between ‘maximum CSA/midforearm’ and shows a statistically significant difference between the ratio and the distal amplitude, below-elbow amplitude, above-elbow amplitude and conduction velocity across the forearm.

We did not find a statistically significant correlation between EDX parameters and ulnar nerve CSA at the midforearm and Guyon’s canal (\(P > 0.05\)).

There was a statistically significant positive correlation between the disease duration and the distal motor latency, ulnar nerve CSA at the ulnar groove, and ulnar nerve CSA at the Guyon’s canal.

### Table 2 Correlation between ulnar nerve cross-sectional area at the ulnar groove and the nerve conduction parameters in the patients’ group

<table>
<thead>
<tr>
<th>Nerve conduction parameters</th>
<th>Below the elbow (between two heads of FCU)</th>
<th>Ulnar groove cross-sectional area</th>
<th>Supracondylar</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(r)</td>
<td>(P) value</td>
<td>(r)</td>
</tr>
<tr>
<td>Distal motor latency</td>
<td>0.481</td>
<td>0.024*</td>
<td>0.543</td>
</tr>
<tr>
<td>Distal amplitude</td>
<td>−0.473</td>
<td>0.026*</td>
<td>−0.607</td>
</tr>
<tr>
<td>Below-elbow amplitude</td>
<td>−0.448</td>
<td>0.037*</td>
<td>−0.561</td>
</tr>
<tr>
<td>Above-elbow amplitude</td>
<td>−0.316</td>
<td>0.152</td>
<td>−0.712</td>
</tr>
<tr>
<td>Conduction velocity above elbow</td>
<td>−0.576</td>
<td>0.005*</td>
<td>−0.562</td>
</tr>
<tr>
<td>Conduction velocity below elbow</td>
<td>−0.408</td>
<td>0.039*</td>
<td>−0.582</td>
</tr>
</tbody>
</table>

*\(P \leq 0.05\) significant.  **\(P \leq 0.01\), highly significant. FCU, flexor carpi ulnaris.

### Table 4 Correlation between disease duration and nerve conduction parameters and ulnar nerve cross-sectional areas in the patients’ group

<table>
<thead>
<tr>
<th>Nerve conduction parameters</th>
<th>Disease duration (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(r)</td>
</tr>
<tr>
<td>Distal motor latency</td>
<td>0.659</td>
</tr>
<tr>
<td>Distal amplitude</td>
<td>−0.463</td>
</tr>
<tr>
<td>Below-elbow amplitude</td>
<td>−0.343</td>
</tr>
<tr>
<td>Above-elbow amplitude</td>
<td>−0.606</td>
</tr>
<tr>
<td>Conduction velocity through the elbow</td>
<td>−0.393</td>
</tr>
<tr>
<td>Conduction velocity through the forearm</td>
<td>−0.490</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ulnar nerve cross-sectional areas at different levels by ultrasound</th>
<th>Disease duration (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guyon’s canal</td>
<td>−0.116</td>
</tr>
<tr>
<td>Midforearm</td>
<td>0.050</td>
</tr>
<tr>
<td>Below the elbow (between two heads of FCU)</td>
<td>0.095</td>
</tr>
<tr>
<td>Ulnar groove</td>
<td>0.591</td>
</tr>
<tr>
<td>Supracondylar</td>
<td>0.098</td>
</tr>
<tr>
<td>Ratio between maximum cross-sectional area and midforearm</td>
<td>0.399</td>
</tr>
</tbody>
</table>

*\(P \leq 0.05\) significant.  **\(P \leq 0.01\), highly significant. FCU, flexor carpi ulnaris.
the ratio between maximum CSA and midforearm CSA ($P \leq 0.05$; Table 4), whereas there was significant negative correlation between disease duration and the distal amplitude, above-elbow amplitude, conduction velocity across the elbow, and the conduction velocity along the forearm ($P \leq 0.05$; Table 4).

In contrast, there was no significant correlation between the disease duration and below-elbow amplitude of ulnar nerve CMAP, ulnar nerve CSA at the Guyon’s canal, midforearm, and below-elbow and supracondylar areas ($P > 0.05$; Table 4).

As regards the sensitivity and diagnostic accuracy of the ulnar nerve CSA, is shown in Table 5, testing the diagnostic accuracy of the ulnar nerve CSAs at different levels and the CSA, using the ROC curve, revealed highest area under the curve for the CSA ratio, CSA above the elbow, CSA at the ulnar groove, and CSA below the elbow (0.9, 0.9, 0.8, and 0.8, respectively). The cut-off value of the ‘maximum CSA/midforearm CSA ratio’ to differentiate between patients and controls was 1.3, with a sensitivity of 86.4% and specificity of 85%. The positive predictive value was 86.4%, and the negative predictive value was of 85% (Table 5).

Ultrasound was able to determine the site of pathology, which was confirmed in transverse (Fig. 3), as well as longitudinal views (Fig. 4).

**Discussion**

Ulnar neuropathy at the elbow is the second most common upper limb entrapment. Proper evaluation of ulnar neuropathy is strongly recommended to determine the optimum management, because incomplete improvement may have functional, psychological and social disabilities.

### Table 5 Results of receiver-operating characteristic curve analysis of the absolute ulnar nerve cross-sectional areas and cross-sectional area ratio

<table>
<thead>
<tr>
<th>Ulnar nerve cross-sectional area by ultrasound</th>
<th>Cutoff</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Area under the curve (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guyon’s canal</td>
<td>&gt; 7</td>
<td>27.3</td>
<td>95</td>
<td>85.7</td>
<td>54.3</td>
<td>55.8</td>
</tr>
<tr>
<td>Midforearm</td>
<td>&gt; 6</td>
<td>50</td>
<td>70</td>
<td>64.7</td>
<td>56</td>
<td>57.5</td>
</tr>
<tr>
<td>Below the elbow (between the two heads of FCU)</td>
<td>&gt; 8</td>
<td>59.1</td>
<td>100</td>
<td>100</td>
<td>69</td>
<td>80.8</td>
</tr>
<tr>
<td>Ulnar groove</td>
<td>&gt; 9</td>
<td>72.7</td>
<td>100</td>
<td>100</td>
<td>76.9</td>
<td>82.0</td>
</tr>
<tr>
<td>Supracondylar</td>
<td>&gt; 8</td>
<td>59.1</td>
<td>100</td>
<td>100</td>
<td>69</td>
<td>92.2</td>
</tr>
<tr>
<td>Maximum cross-sectional area and midforearm</td>
<td>&gt; 1.3</td>
<td>86.4</td>
<td>85</td>
<td>86.4</td>
<td>85</td>
<td>92.5</td>
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</table>

FCU, flexor carpi ulnaris; NPV, negative predictive value; PPV, positive predictive value.

**Figure 3**

A transverse scan of the left ulnar nerve at the supracondylar level showing ulnar nerve entrapment. The nerve shows normal echotexture. The nerve Cross sectional area (CSA) is 0.27 cm².
Although the electrophysiological tests are important indispensable tools in the diagnostic workup of ulnar neuropathy at the elbow, they have some limitations.

The aim of this study was to assess the value of neuromuscular ultrasound in ulnar neuropathy at the elbow and assess its correlation with the EDX studies.

As regards ultrasound findings, the mean CSA of the ulnar nerve in our control group was 5.45 mm$^2$ at the Guyon’s canal, 5.8 mm$^2$ at the midforearm, 5.95 mm$^2$ at the cubital tunnel, 6.50 at the ulnar groove and 5.80 mm$^2$ at the supracondylar area. Our measurements agree with the published reference values of ulnar nerve CSA [9].

Mean values of ‘maximum enlargement/midforearm’ CSA ratio in our study was 1.13, and the cutoff value of the CSA ratio was 1.3. This is quite similar to the results obtained by Cartwright and Walker [10], who measured CSA at the cubital tunnel and another nonaffected site and calculated the ratio between them. The cutoff value was 1.4 in their study.

Moreover, Gruber et al. [11] found a cutoff value of CSA ratio between “CSA of maximum enlargement/midhumeral CSA” to be 1.4; although they used different methodology and number of patients, the CSA area ratio is similar to ours.

This study included fewer patients, and we measured the CSA ratio and the absolute CSA differently. We measured the ratio between CSA at maximum enlargement and midforearm. However, Gruber et al. [11] calculated the CSA ratio between the cubital tunnel and the midhumeral area and found a CSA ratio more than 1.4 to be diagnostic for cubital tunnel with a specificity of more than 95.

In this study, we found a significant difference in CSA at the ulnar groove, cubital tunnel and supracondylar levels between patients and control groups. The CSA was significantly larger in patients compared with the controls. Similarly, Gruber et al. [11] also found a significant difference in CSA at the ulnar groove, cubital tunnel and supracondylar levels in their patients compared with their controls. In contrast, we did not find a significant difference in CSA at Guyon’s canal and the midforearm between our patients and controls, which denotes that, in patients with ulnar nerve entrapment, the enlargement is focal at the elbow region.

In this study, there was a negative correlation between the maximum ulnar nerve CSA/midforearm CSA ratio and CMAP amplitude and conduction velocity (CV), whereas there was no significant correlation between CSA ratio and the DML. The negative correlation between CSA and amplitude and CV denote that nerve

Figure 4

A longitudinal scanning of Right Ulnar nerve entrapment at the ulnar groove: arrow points to the site of entrapment. UN, ulnar nerve.
enlargement is related to the degree of axonal affection and demyelination, and thus neuromuscular ultrasound (NMUS) can be useful in the assessment of severity of entrapment.

There was a statistically significant positive correlation between ulnar nerve CSA values at both the ulnar groove and below the elbow and the DML; this means that, as the CSA increases, the DML prolongs, whereas there was a statistically significant negative correlation between ulnar CSAs at below the elbow, ulnar groove and supracondylar sites with below-elbow amplitude. There was a statistically significant negative correlation between ulnar CSA at below the elbow and ulnar groove sites with each of the following EDX parameters: DML, CMAP distal amplitude and conduction velocity. There was also a highly significant negative correlation between ulnar CSA at the ulnar groove and above-elbow amplitude, which denotes that the nerve enlarges as the amplitude decreases and is related somehow to the degree of axonal loss. This agrees with the results obtained by Volpe and colleagues who found a significant correlation between maximum CSA and severity estimated by nerve conduction velocity (NCVs).

In contrast, there was no significant correlation between the disease duration and below-elbow amplitude of ulnar nerve CMAP, ulnar nerve CSA at the Guyon’s canal, midforearm, and below-elbow and supracondylar areas (P>0.05).

The ultrasound detected changed echogenicity (anechoic) of the ulnar nerve in one of 22 elbows, in three abnormal mobility cases (two subluxated and one dislocated), in two patients with accessory anconeus epitrochlears muscle, and in one patient who had a compressing mass at the ulnar groove (Fig. 5).

ROC curve results demonstrated high diagnostic ability of absolute CSA and the ratio between ‘maximum enlargement/midforearm CSA’, making it a useful tool to differentiate between patients and controls.

Limitations of the study include the small number of patients in each group and the lack of follow-up of the patients to track the sonographic and EDX changes postconservative or surgical management. Another limitation is that we did not assess the sonographic changes in the ulnar-innervated muscles.

Conclusion
Our limited data suggest that NMUS examination plays a potentially important role in the assessment of ulnar neuropathy at the elbow; it can localize the lesion and detects the site of maximal enlargement, which could be of value if surgical intervention is required. It detected changed echogenicity and mobility, giving an idea about the ongoing pathology. In addition, it may reveal the causative pathology such as accessory anconeus epitrochlears muscle or compressing masses. On the basis of
ROC curve analysis, its diagnostic ability is high with good sensitivity and specificity and thus is able to differentiate between patients and healthy individuals. Moreover, it correlates with the parameters of NCS and thus can give a clue about severity of the entrapment.

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**Conflicts of interest**
There are no conflicts of interest.

**References**
Clinical significance of interleukin 27 serum concentration in patients with systemic sclerosis: relation to clinical, laboratory, and radiological parameters

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**Background**
Interleukin 27 (IL27) is a cytokine that belongs to IL12 family and it is mainly produced by antigen presenting cells. IL27 binding to its receptor leads to activation of many intracellular signaling pathways that can exhibit a wide variety of immunomodulatory actions.

**Aim of the work**
The current study aimed to determine IL27 concentrations in the sera of SSc patients and to assess the relation between these concentrations and the various clinical, laboratory and radiological disease parameters.

**Methods**
We measured serum IL27 concentrations in 31 SSc patients and 20 controls. The patients were subjected to detailed history and clinical evaluation. In SSc patients, modified Rodnan skin score (MRSS) was used to assess the skin thickness and pulmonary involvement was assessed by high resolution computerized tomography (HRCT) and forced vital capacity (FVC) assessment.

**Results**
IL27 serum concentrations in diffuse (median, 302.8; 101.6-1034.4 ng/L) and limited (median, 385; 109-826.3 ng/L) subtypes of SSc showed a significant elevation (\(P < 0.001\)) compared to its concentrations in the controls (median, 104.2; 51-184.2 ng/L). SSc patients with elevated IL27 serum concentrations had significantly lower forced vital capacity (FVC) than those with normal IL27 serum concentrations (\(p=0.04\)). Also, serum level of sCD163 significantly correlated with MRSS (\(r=0.48, p=0.0064\)) and FVC (\(r=-0.6, p=0.0005\)).

**Conclusion**
Patients with systemic sclerosis have significantly increased serum IL27 concentrations that remarkably associated with significant cutaneous and pulmonary involvement signifying that it could be a beneficial biomarker that reflects disease severity and implies a possible pathogenic role in SSc.

**Keywords:**
Interleukin 27, pulmonary fibrosis, systemic sclerosis, rodnan skin score

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**Introduction**
Systemic sclerosis (SSc) is a chronic multisystem complex autoimmune disorder that has the characteristic pathological features of immune dysregulation and microvascular involvement and ends with organ fibrosis [1]. It involves not only the skin but also many visceral organs such as the lungs, the heart, kidneys, and the gastrointestinal tract, with a varying degree of severity. Moreover, the magnitude of visceral involvement is usually reflected by the rate of progression of skin fibrosis [2].

The pathophysiology of SSc remains not fully understood. It is believed that the interaction between the genetic [3] and environmental elements causes an alteration of the immunological response that represents the initial phase of development of SSc [4].

Dysregulation of the adaptive immunity, involving the presence of pathogenic autoreactive T lymphocytes and the autoantibody production by B lymphocytes, was thought to be the only mechanism of immune dysregulation in SSc [5], but recently, there is increased interest about the role of toll-like receptors, a key player of innate immunity, in the pathogenesis of SSc [6].

Interleukin (IL) 27 is a cytokine that belongs to IL12 family and it has a heterodimeric structure [7]. It was thought to be produced only by antigen-presenting...
cells, in particular monocytes, dendritic cells, and macrophages, but now it is recognized to be expressed by a wide range of other cells such as keratinocytes and B and T lymphocytes [8,9]. The receptor of IL27 is formed of glycoprotein 130 and IL27Ra subunits [7], and it is distributed on a broad range of cells such as lymphocytes, endothelial cells, macrophages, and mast cells [10]. IL27 binding to its receptor leads to activation of many intracellular signaling pathways that can exhibit a wide variety of immunomodulatory actions according to the nature of stimulated cell [11].

Few studies investigated the role of IL27 in rheumatic autoimmune diseases such as rheumatoid arthritis [12], systemic lupus erythematosus [13], SSC [14], and psoriasis [15], and the exact functional role of IL27 in these disorders is not fully clear. It is found to exhibit a ‘functional antagonism’ as IL27 can suppress inflammatory reactions through its ability to downregulate the release of IL17 [16] and increase the expression of IL10 [7]. On the contrary, IL27 inhibits the induction and differentiation of regulatory T lymphocyte (Treg) which is known to have a main role in maintenance of self-tolerance [17]. Moreover, it can enhance antibodies production by B lymphocytes [18] and stimulate follicular T helper lymphocytes [10].

The current study aimed to determine IL27 concentrations in the sera of patients with SSc and to assess the relation between these concentrations with various clinical, laboratory, and radiological disease parameters.

Participants and methods

Participants

This study was conducted at Rheumatology, Rehabilitation and Physical Medicine Department, Benha University Hospital and Benha Insurance Hospital during the period from February 2016 to July 2018. The study was conducted on two groups: the first group included 31 patients with SSc diagnosed according to the 2013 classification criteria proposed by ACR/EULAR [19], and the second group included 20 apparently healthy volunteers with comparable age and sex who were registered in this study as a control group.

Patients with SSc were separated into two subcategories according to LeRoy et al. [20] criteria depending on magnitude of skin involvement: diffuse SSc included 19 patients and limited SSc included 12 patients. Patients having conditions that can affect concentrations of IL27 such as rheumatoid arthritis, multiple sclerosis, other autoimmune disorders, recent infection, and malignancy were excluded.

Detailed medical history was recorded and comprehensive examination was executed with emphasis on skin manifestations, Raynaud phenomenon, musculoskeletal involvement, and manifestations suggestive of involvement of internal organs such as the lung, the heart, gastrointestinal, and the kidney, as demonstrated by Steen et al. [21]. Modified Rodnan score (MRS) was used by assessment of the thickness of the skin in 17 anatomical areas [22].

Laboratory and radiological assessment

Venous samples were extracted for measurement of erythrocyte sedimentation rate, C-reactive protein, complete blood count, liver enzymes, and renal function. Moreover, antinuclear antibodies were tested using indirect immunofluorescence kits (IMMCO Diagnostics Inc., New York, USA) whereas antitopoiso merase I (Cusabio, Hubei, China) and anticientromere (My Biosource, San Diego, California, USA) antibodies were measured using the ELISA technique. Calcinosis was assessed using plain radiography of both hands, and high-resolution computed tomography of the lung, forced vital capacity (FVC), and the ratio between forced expiratory volume in first second (FEV1) and FVC (FEV1%) were used to assess pulmonary affection. Moreover, pulmonary artery systolic pressure was measured using Doppler echocardiography.

This study was approved by the ethics committee of Faculty of Medicine, Benha University, and all participants signed a written informed consent.

Assessment of IL27 serum concentrations

IL27 concentrations were measured in serum samples obtained from patients with SSc and healthy controls. The serum samples were centrifuged and stored at −40°C till testing. IL27 assay was performed following the manufacturer’s instruction using ELISA kits provided by Sunred (Shanghai, China). The range of assay is 6.5–2000 ng/l.

Statistical analyses: the 18th version of the statistical package for the social sciences program (SPSS; SPSS Inc., Chicago, Illinois, USA) was used to statistically analyze the data of this study. Mean±SD is the term used to summarize quantitative data, whereas percentages and frequencies were used to describe qualitative data. The Student t-test was performed to compare means of two groups with normally distributed data, whereas Fisher’s exact test was used
to detect differences in frequencies. The differences of nonparametric data between two groups was detected using Mann–Whitney test. The diagnostic performance of IL27 serum concentrations for FVC of our patients with SSc was examined using the receiver operating characteristic curve (classification variable is considered positive if FVC <80%). Area under the curve, best cut-off point, and its sensitivity and specificity were estimated. The correlations between IL27 levels and various SSc-related variables were evaluated using the test of Pearson’s correlation coefficient. P value less than 0.05 was accepted to be statistically significant.

**Results**

The mean age of patients with SSc was 33.13±9.5 years (range: 18–54 years) and was comparable with that of the healthy control 36.1±8.33 (range: 20–51 years). The sex of our patients with SSc (female 27 : male 4) was also matched with that of the control (female 17 : male 3). Moreover, there was no significant difference (P=0.14) in the mean of disease duration between patients with SSc with diffuse (3.26±1.99 years) and limited (4.67±2.9) subtypes.

IL27 concentrations in the serum of patients with SSc (median: 319.6; range: 101.6–1034.4 ng/l) were significantly higher (P<0.001) than its concentrations in the controls (median: 104.2; 51–184.2 ng/l).

Moreover, serum concentrations of IL27 in diffuse (median: 302.8; 101.6–1034.4 ng/l) and limited (median: 385; 109–826.3 ng/l) subtypes of SSc showed a significant elevation (P<0.001) compared with its concentrations in the controls (Fig. 1). No significant difference was found in the median of IL27 serum concentrations between patients with diffuse SSc and those with limited SSc (P=0.61).

Nineteen (61.29%) patients with SSc had elevated IL27 concentrations in the serum, considered if more than the mean plus 2 SD of its concentration in the serum of healthy controls (176.24 ng/l), whereas 12 (28.71%) patients had normal serum IL27 concentrations. Patients with SSc who had elevated serum concentrations of IL27 had a significant increase in MRS (20.16±6.53) compared with those with normal IL27 serum concentrations (14.08±7.09) (P=0.02). Moreover, FVC was significantly lower (P=0.04) in patients with SSc with elevated IL27 serum concentrations (84.53±9.37) compared with those with normal serum concentrations of IL27 (93.42±14.05). There was no significant difference between patients with SSc with elevated and normal IL27 serum concentrations regarding disease duration, demographic, clinical, laboratory, or radiological data (Table 1).

Seventeen (54.84%) of our patients with SSC were receiving treatment at the time of their inclusion in the study, with 16 (51.61%) patients receiving Figure 1

![Distribution of interleukin 27 serum concentrations among patients with diffuse and limited SSc and healthy controls. SSc, systemic sclerosis.](image)

*Significant at P<0.05.
corticosteroids, eight (25.8%) patients receiving cyclophosphamide, seven (22.58%) patients receiving azathioprine, and two (6.45%) patients receiving mycophenolate mofetil, whereas 14 (45.16%) patients with SSc were recently diagnosed and did not receive corticosteroids or immunosuppressive drugs at the time of their enrollment in the study.

IL27 serum concentration of patients with SSc who were treated with corticosteroids and immunosuppressive medications (317.41±209.91 ng/l) was lower than its concentration in those who did not receive treatment (421.05±288.28 ng/l), but this difference was not statically significant ($P=0.26$).

Patients with SSC with pulmonary fibrosis (PF), as evaluated with high-resolution computed tomography, had significantly higher ($P=0.023$) serum IL27 concentrations (median: 405.8; 103.4–1034.4 ng/l) than those who did not have PF (median: 169.1; 103.4–826.3 ng/l) (Fig. 2).

The receiver operating characteristic curve between serum concentrations of IL27 and FVC revealed area under the curve of 0.755 and the cut off for the decrease of FVC less than 80% was 534 ng/l with sensitivity of 60% and specificity of 90.84% (Fig. 3).

Serum IL27 concentrations had a significant positive correlation with MRSS ($r=0.48$, $P=0.0064$) whereas it revealed a significant negative correlation with FVC ($r=-0.6$, $P=0.0005$) (Table 2). IL27 did not show any significant correlation with other clinical and laboratory parameters of our patients with SSc.

Discussion
There is a strong evidence of early activation of the immune cells as an essential component of the pathophysiology of SSc [23]. Infiltration of the skin by immune cells, mainly T helper (Th) type 2 lymphocytes and macrophages, is considered the initial event in SSc course that is followed later by fibrosis of the skin [24].

Fibrosis can be induced by Th2 lymphocytes through numerous mechanisms. In addition to its ability to activate fibroblasts by direct contact process [23], Th2 lymphocytes also secretes several cytokines that have a

<table>
<thead>
<tr>
<th>Table 1 Clinical, laboratory, and radiological characteristics of patients with systemic sclerosis with elevated or normal interleukin 27 serum concentrations</th>
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<tr>
<td>Patient with elevated IL27 levels ($n=19$)</td>
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<td>Continuous variables (mean±SD)</td>
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<td>CRP (mg/dl)</td>
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<td>Immunosuppressive medications</td>
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CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IL, interleukin; MRS, modified Rodnan score; PASP, pulmonary artery systolic pressure. $P<0.05$, significant.
profibrotic activity, such as IL4 [25] and IL13 [26], which are known to upregulate secretion of transforming growth factor-β, a key mediator of fibrosis in SSC, by the macrophages.

IL27 is an interesting mediator as it has multiple effects on the immune system. It enhances Th1 lymphocytes differentiation whereas downregulates the development of Th2, Treg, and Th17 lymphocytes through its effect on

Figure 2

Distribution of interleukin 27 serum concentrations among patients with SSc with and without pulmonary fibrosis. PF, pulmonary fibrosis; SSc, systemic sclerosis. *Significant at $P<0.05$.

Figure 3

Receiver operating characteristic curve evaluating the validity of the interleukin 27 serum interleukin 27 concentrations in prediction of forced vital capacity in patients with systemic sclerosis. Area under the curve was 0.755, 95% confidence interval.
We found patients with SSc to have a significant elevation \((P<0.001)\) in IL27 serum concentrations compared with its concentrations in the serum of controls, and this increase was also observed in both the diffuse and limited subtypes. Moreover, we found IL27 to be associated with more severe skin involvement as it correlates positively \((r=0.48, P=0.0064)\) with skin thickness scores, which were significantly higher \((P=0.02)\) in patients with SSc who had elevated serum concentrations of IL27. These results were consistent with the findings of Yoshizaki et al. [14] who found elevated expression of IL27 in the serum as well as the skin of patients with SSc. In addition, receptors of IL27 were highly expressed in the fibroblasts of patients with SSc compared with those of the controls and a positive correlation was established between MRS and IL27.

Pflanz et al. [28] found activated fibroblasts to have increased expression of IL27R, and the binding of IL27 to its receptors enhances more activation of fibroblasts with increased collagen synthesis.

Our patients with SSc, who had PF, had a significant elevation \((P=0.023)\) in their serum concentrations of IL27 compared with those without PF. Moreover, FVC was significantly lower \((P=0.04)\) in patients with SSc with elevated IL27 serum concentration than those with normal concentrations, and a significant negative correlation \((r=−0.6, P=0.0005)\) was found between serum concentrations of IL27 and FVC in our patients with SSc. Yoshizaki et al. [14] established the association of IL27 and PF in their patients with SSc, as they found a negative correlation between serum IL27 and FVC and carbon monoxide diffusion capacity.

It is postulated that IL27 constitutes a bridge between innate and acquired immune systems [10], as Kopiński et al. [29] found a positive correlation between IL27 concentrations and CD4+ and total lymphocytic count in the fluid of bronchoalveolar lavage obtained from 12 patients with idiopathic PF, and they suggested that IL27 may be produced locally by CD4+ and CD8+ cells. Nevertheless, Su et al. [30] revealed that IL27 stimulates innate immunity through the expanded expression of toll-like receptor 4 in pulmonary fibroblasts leading to increased secretion of lipopolysaccharide-induced cytokines such as IL6 and IL8.

We could not find a significant relation between disease duration and IL27 concentrations in our patients with SSc. In contrast, Yoshizaki et al. [14] found IL27 to be higher in the early phase of SSc and suggested a possible role in the pathogenesis of early SSc. This can be attributed to the difference in sample size and disease duration between the two studies. Moreover, we did not follow-up our patients with SSc to examine the precise effect of duration of SSc on IL27 concentrations.

Although many studies investigated the role of IL27 in PF in various conditions with pulmonary involvement [14,29,31], only one previous study evaluated the potential role of IL27 in SSc [14]. Limitations of our study were the relative small sample size of our patients with SSc, and some of our patients were already treated at the time of study. Moreover, we did not follow-up our patients over sufficient period of time to investigate the role of IL27 in the progression of SSc.

In conclusion, patients with SSc have significantly increased serum IL27 concentrations that are remarkably associated with significant cutaneous and pulmonary involvement, signifying that it could be a beneficial biomarker that reflects disease severity and implies a possible pathogenic role in SSc.

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 Nil.

### Conflicts of interest
 There are no conflicts of interest.

### References

Relation of ischemia-modified albumin to disease manifestations and activity in Egyptian patients with Behçet’s disease

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Aim of work
To determine level of ischemia-modified albumin (IMA) in patients with Behçet’s disease (BD) and to assess its role in disease manifestations and activity.

Patients and methods
The study included 48 patients with BD and 38 matched controls. Disease activity was estimated by the BD current activity form. Serum IMA was measured.

Results
Mean age of the patients was 33.8±7.9 years. There were 42 males and six females, and the disease duration was 52.9±48.8 months. The serum IMA level was significantly increased in the patients with BD (50.9±12.9 U/ml) compared with the control (7.76±1.6 U/ml) (*P*<0.001). There was a statistically significant association between IMA level and disease activity, with high mean IMA level among active cases (*P*=0.01). There was no statistically significant association between IMA level and any of other clinical characteristics in patients with BD. Sensitivity and specificity test for IMA level in detection of cases illustrated accuracy of 98.5% with sensitivity 95.8% and specificity 78.9% at cutoff value of 9.4 U/ml.

Conclusion
There is growing evidence indicating the role of oxidative stress in BD. IMA is accepted as an essential marker of oxidative stress in patients with BD. It has a potential diagnostic value for the detection of the disease. Furthermore, it correlates with the disease activity.

Keywords:
Behçet’s, disease, ischemia-modified albumin, oxidative stress

Introduction
Behçet’s disease (BD) is a recurring inflammatory multisystem disease; it is characterized by recurrent oral aphthosis, genital ulceration, ocular and variable skin is frequently associated with vascular thrombosis and formation of arterial aneurysms [1]. Male individuals are more frequently affected compared with female individuals, and it is more common in the second to fourth decade of life [2].

The etiology, pathogenesis, and mechanisms that underlie vascular disease occurring in BD are unknown. Alterations of the immunoregulatory system have been suggested to play an important role; many proinflammatory cytokines and B-cell activation have been involved in the pathogenesis of the disease [3,4]. Endothelial dysfunction and disturbed neutrophil functions, such as phagocytosis, chemotaxis, and generation of reactive oxygen species (ROS) have been suggested to be factors in the pathophysiology and etiology of BD. Overproduction of ROS with decreased level of antioxidant defense system was found to occur in BD, leading to increase of oxidative stress [5].

Ischemia-modified albumin (IMA) is recently accepted as a biomarker of ischemia and oxidative stress. It is broadly studied in many types of ischemic diseases [6–8]. In addition, its level is found to be elevated in diseases accompanied by vascular endothelial cell dysfunction [9].

The aim of this study is to determine levels of IMA in patients with BD and to assess its role in disease manifestations and activity.

Patients and methods
A total of 48 patients with BD and 38 age-matched and sex-matched healthy volunteers as controls were recruited in the study. BD diagnosis was made based on The International Criteria for Behçet’s Disease [10].

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The study was approved by the Local Research Ethical Committee of Fayoum University and conforms to the 1995 Declaration of Helsinki. After obtaining informed consent from all of the study participants, complete systemic and ophthalmologic examinations were done for all patients to define systemic and ophthalmologic involvement. The current activity form of Behçet’s disease was assessed [11]. Patients having any systemic disease were excluded from the study.

Serum IMA was measured quantitatively using the Human IMA ELISA Kit (Sun Long Biotech Co. Ltd) according to the manufacturer’s protocol. To obtain serum, blood samples were centrifuged at 3000 rpm for 10 min and stored at −80°C. IMA levels were detected by adding 40 μl of sample dilution buffer and 10 μl of sample (dilution factor is 5) in sample wells; empty well was left as blank control. Closure plate membrane was used to cover wells to be incubated at 37°C for 30 min. According to the manufacturer’s protocol, dilution of the concentrated buffer with distilled water washing was done. The plate was incubated and washed after adding 50 μl HRP-conjugate reagents to each well excluding the blank control well. Then, 50 μl of chromogen solution A and 50 μl of chromogen solution B were then added to each well for 15 min in the dark. The color reaction was terminated by adding 50 μl of stop solution to each well to terminate the reaction. By comparing the absorbance values at 450 nm using a Microtiter Plate Reader, IMA concentrations were measured.

Statistical analysis
Data were analyzed by statistical package of social science software, version 18, in Windows 7 (Milton, QLD, Australia). Simple descriptive analyses in the form of numbers and percentages were used for qualitative data, and arithmetic means as central tendency measurement and standard deviations as measure of dispersion were used for quantitative parametric data. Quantitative data included in the study was first tested for normality by one-sample Kolmogorov–Smirnov test in each study group, and then inferential statistic tests were selected. For quantitative parametric data, independent Student’s t test was used for comparing measures of two independent groups of quantitative data. For qualitative data, χ² test was used to compare two or more than two qualitative groups. Bivariate Pearson’s correlation test was used to test association between variables. Sensitivity and specificity of IMA level in diagnosis of Behçet’s disease with receiver operating characteristic (ROC) curve. The P value less than or equal to 0.05 was considered as the cut-off value for significance.

Results
The mean age of study group was 33.8±7.9 years, with 87.5% were males and 12.5% were females. The patients’ characteristics are presented in Table 1. The serum level of IMA was significantly increased in the group of patients with BD (50.9±12.9 U/ml) compared with the control group (7.76±1.6 U/ml) (P<0.001) (Fig. 1).

There was a statistically significant association between IMA level and disease activity, with high mean IMA level among active cases (P=0.01). There was no statistically significant association between IMA level and any of other clinical characteristics of patients with BD (Table 2). Moreover, there was no statistically significant correlation (P value more than 0.05) between IMA level and any of age of the patients or duration of the disease (r=0.03, P=0.9 and r=−0.40, P=0.06, respectively), which indicated that there was no effect of these variables on IMA level.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Behçet’s disease patients (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.8±7.9</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>52.9±48.8</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (87.5)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (12.5)</td>
</tr>
<tr>
<td>Positive family history</td>
<td>10 (20.8)</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td></td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>18 (37.5)</td>
</tr>
<tr>
<td>Genital ulcers</td>
<td>4 (8.3)</td>
</tr>
<tr>
<td>Ocular</td>
<td>16 (33.3)</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>14 (29.2)</td>
</tr>
<tr>
<td>Pathergy positivity</td>
<td>22 (45.8)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td>Vascular</td>
<td>8 (16.7)</td>
</tr>
<tr>
<td>Laboratory investigations</td>
<td></td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>11.4±1.3</td>
</tr>
<tr>
<td>WBC (x10³/mm³)</td>
<td>6.8±1.7</td>
</tr>
<tr>
<td>Platelets (x10³/mm³)</td>
<td>365.4±84.3</td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>37.4±28.8</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>27.9±16.5</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>24.2±23.4</td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>3.4±0.35</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.83±0.17</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>34 (70.8)</td>
</tr>
<tr>
<td>Colchicine</td>
<td>28 (58.3)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>14 (29.2)</td>
</tr>
<tr>
<td>BDCAF</td>
<td>2.13±1.3</td>
</tr>
</tbody>
</table>

Data are presented as n (%) and mean±SD. ALT, alanine transaminase; AST, aspartate transaminase; BDCAF, Behçet’s disease current activity form; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; WBC, white blood cells.
Sensitivity and specificity test for IMA level in detection of cases illustrated accuracy of 98.5% with sensitivity 95.8% and specificity 78.9% at cutoff value of 9.4 U/ml (Fig. 2).

**Discussion**

BD is a systemic relapsing inflammatory disease; vascular involvement commonly occurs and predisposes to thrombosis [12]. Oxidative stress plays a major role in endothelial dysfunction and vascular injury [13,14].

ROS and lipid peroxides have been involved in the pathogenesis of various immune-mediated diseases [15,16]. IMA has been studied in diseases associated with oxidative stress and endothelial dysfunction [9,17,18]. Moreover, it is considered as a biomarker of ischemia, oxidative stress, and endothelial dysfunction [9,19].

Levels of IMA are increased as a result of oxidative stress induced during inflammation. As a marker of oxidative stress, IMA is assumed to be connected to the pathogenesis of BD [20]. It is a metabolic variant of the protein which is generated during acute ischemic conditions owing to a free radical damage, resulting in decrease in the albumin-binding capacity for transition metals, such as cobalt, copper, and nickel [19,21]. The binding capacity of the albumin to transition metals can also be modified as a result of oxidative stress [22].

In the present study, IMA level was detected, and the association between it and specific clinical features and disease activity of BD was investigated, and it was found that level of serum IMA was significantly increased in the patients with BD compared with the control. In addition, it significantly correlated with Behçet disease current activity form.

In accordance with the current study, Kılcı et al. [23] found that the IMA values of patients with BD during the active phase of the disease were significant as compared with the inactive phase and with the control group. Moreover, a study by Ozyazgan et al.

**Table 2** Serum ischemia-modified albumin according to the presence and absence of clinical characteristics in patients with Behçet’s disease

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>IMA (U/ml) in patients with BD (N=48)</th>
<th>Presence</th>
<th>Absence</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td>13.5±2.7 12.6±2.1</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral ulcer</td>
<td>12.8±2.5 12.8±2.1</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital ulcers</td>
<td>14.2±3.5 12.7±2.2</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular</td>
<td>12.7±2.1 12.8±2.4</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin lesions</td>
<td>12.1±2.3 13.1±2.2</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive pathergy</td>
<td>12.6±2.1 12.9±2.4</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>15.3±0 12.7±2.2</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>12.2±2.9 12.9±2.1</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid</td>
<td>12.8±2.2 12.7±2.4</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colchicine</td>
<td>12.7±2.2 12.9±2.3</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>13.0±1.9 12.7±2.4</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDCAF</td>
<td>15.0±2.6 13.1±2.4</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. BD, Behçet’s disease; BDCAF, Behçet’s disease current activity form; IMA, ischemia-modified albumin. Bold values are significant at P value less than 0.05.
showed higher level of IMA in patients with BD during the active state of the disease.

Capkin et al. [18] concluded that IMA is a marker for patients with BD with vascular affection. They found that IMA levels were statistically significantly higher in patients with BD with vascular manifestations. However, the present study did not confirm this association.

**Conclusion**

There is growing evidence indicating the role of oxidative stress in BD. IMA is accepted as an essential marker of oxidative stress in patients with BD. It has a potential diagnostic value for the detection of the disease. Furthermore, it correlates with the disease activity.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**


Ultrasonographic features of tibialis posterior tendon in rheumatoid arthritis patients with pes planovalgus
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Aim
The aim of this study was to assess the relationship between ultrasonographic features of tibialis posterior (TP) tendon in rheumatoid arthritis (RA) patients and associated pes planovalgus (PPV) foot deformity.

Patients and methods
This study included 20 (40 feet) RA patients with PPV and ultrasound-proven TP tenosynovitis. The following variables were recorded for patients: the number of tender and swollen foot joints count, foot posture index (FPI), Health Assessment Questionnaire, and Disease Activity Score 28 (DAS28). FPI is a clinical tool used to quantify the degree to which a foot is pronated, neutral, or supinated using the set criteria. Patients underwent high-resolution ultrasound of the TP tendon. Measurement of tendon diameter was recorded in the retromalleolar region. The presence of fluid around the TP tendon and levels of power Doppler signal (PDS) were assessed.

Results
High disease activity was detected in patients (mean DAS28 of 5.89). Eighteen (45%) feet had thickened transverse diameter and 15 (37.5%) feet had thickened longitudinal diameter. Twenty-three feet showed PDS. Nineteen feet had fluid around the tendon, detected only in the retromalleolar region. Regarding FPI, 14 feet were mild to moderate pronated feet and 26 feet were highly pronated feet. There were direct correlation between FPI and both DAS28 (p=0.05) and transverse diameter thickness (p=0.01). Highly pronated feet had higher DAS28 (p=0.03), increased transverse diameter thickness (p=0.04), more detection of fluid around the TP tendon (p=0.005) as well as higher incidence of PDS around the TP tendon (p=0.002).

Conclusion
Higher degree of pronation in RA feet with PPV is associated with ultrasonographic increased tendon thickness, PDS, and fluid around TP tendon. Early diagnosis and intervention for TP tenosynovitis may prevent progressive PPV foot deformity.

Keywords:
foot posture index, pes planovalgus, rheumatoid arthritis, tenosynovitis, tibialis posterior

Introduction
Rheumatoid arthritis (RA) is the most common inflammatory arthritis, affecting ∼1% of the world’s population [1]. Approximately 90% of patients with RA will report foot-related symptoms at some time during the disease course [2]. Tenosynovitis is one of the key features of the clinical pattern in these patients [3]. The most common ankle tendons affected by tenosynovitis is the tibialis anterior followed by the tibialis posterior (TP) [4]. Tibial posterior tendon stabilizes the hindfoot against valgus and eversion forces. It is a powerful subtalar joint supinator and acts as a support of the medial longitudinal arch (MLA). Dysfunction of the TP tendon following degeneration and rupture results in progressive destabilization of the hindfoot and the midfoot [5]. However, lesser degrees of TP tendon dysfunction is considered as a factor contributing to heel valgus and flatfoot deformities in RA patients. This condition results in significant foot pain and walking disability [6]. Flat feet are also associated with knee pain and cartilage damage [7]. Furthermore, tenosynovitis and associated flat feet could result in the occurrence of tarsal tunnel syndrome [8].

Both mechanical and inflammatory factors are believed to be involved in the development of pes planovalgus (PPV) foot deformity and TP tenosynovitis in RA patients [9]. However, there is still a controversy...
around whether the planovalgus deformity is due to TP tenosynovitis and/or subtalar and midfoot arthritis and synovitis [10].

Musculoskeletal ultrasound (US) is important for the diagnosis and monitoring treatment efficiency in patients with inflammatory rheumatic diseases [11]. It is a reproducible tool for evaluating and monitoring tenosynovitis in RA. US can assess tendon features, detect synovitis and power Doppler signal (PDS) can detect the presence of hyperemia suggestive of active inflammation [12,13]. It can also identify residual subclinical inflammation in clinically silent patients [14]. Accordingly, this work aimed at assessing the US features of TP tenosynovitis, in RA patients having PPV foot deformity, and studying their relationship to pes planus foot posture.

Aim
The aim of this study was to study US features of TP tendon in RA patients having PPV foot deformity using high-resolution US and assess the relationship of these US features to pes planus foot posture.

Patients and methods
The study included 20 RA patients (diagnosed based on the 2010 American College of Rheumatology criteria [15]) with PPV foot deformity and US features of TP tenosynovitis. Inclusion criteria for patients included: passively correctable PPV deformity (valgus rearfoot alignment, MLA collapse, and medial bulging of the talonavicular joint) [16,17], in conjunction with abduction of the forefoot in relaxed standing [18] and US-confirmed tenosynovitis ‘defined as hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath which may or may not exhibit Doppler signal’ [19]. The nature of this study was explained to all studied patients. Informed consents were obtained from all patients. Research protocol was approved by the local ethics committee.

Demographic data and clinical assessment
The studied patients’ age, sex, and disease duration were also assessed. The following clinical variables were recorded: tender and swollen foot joint count and global disability using the Health Assessment Questionnaire (HAQ) [20]. Disease activity was recorded using the Disease Activity Score in 28 joints (DAS28) [21], including erythrocyte sedimentation rate within 2 weeks of assessment. Visual analog scale (100 mm) was used to record foot pain, general health, and arthritis pain. Foot posture was recorded using the foot posture index (FPI) [22,23].

The FPI [22–24] is a diagnostic clinical tool for quantifying the degree to which a foot can be considered to be in a pronated, supinated, or neutral position. The FPI is a six-item foot posture assessment with the patient standing relaxed in a bipedal position. The six items of the FPI include talar head palpation, supra and infra lateral malleolar curvature, calcaneal frontal plane angle, prominence in the region of the talonavicular joint, congruence of the MLA, and abduction/adduction of the forefoot on the rearfoot alignment. Each item is scored on a five-point scale of between −2 and +2 and provides a total sum of all items between −12 (highly supinated) and +12 (highly pronated). Accordingly, positive score values [24] indicate a pronated posture (+6 to +9 is pronated, ≥+10 is highly pronated), negative score values indicate a supinated overall foot posture, while for a neutral foot the final FPI score should lie somewhere around 0 (0 to +5) [24].

Ultrasound assessment of tenosynovitis
For the assessment of tenosynovitis, high-resolution US was performed by a single experienced sonographer (experienced radiologist) in a governmental institution using Toshiba Xario 200 Ultrasound machine with dedicated US linear musculoskeletal US probe 14–18 MHz (Toshiba, Tokyo, Japan). The TP tendon was viewed bilaterally and images were recorded along the length of the tendon at three locations: medial malleolus, navicular insertion, and midway between the two points. Measurement of tendon diameter was recorded in the retromalleolar region and compared with normative data published in the literature [25,26]. Presence of fluid around TP tendon, which is suggestive of active inflammation, was also recorded. In addition, PDS [27] was recorded and graded using a four-point semiquantitative scale (absent/minor/moderate/major) [28].

Statistical analysis
Statistical analyses were performed using IBM SPSS software package, version 20.0 (IBM Corp., Armonk, NY) [29]. Qualitative data were described using number and percent. Quantitative data were described using mean, SD, and range.

The distributions of quantitative variables were tested for normality using Kolmogorov–Smirnov test.

The raw data were compared between patients and control groups using Student’s t-test for normally distributed variables and Mann–Whitney test for abnormally distributed variables. The
statistical significance level was set at \( p \) value less than 0.05.

Comparison between different groups regarding categorical variables was tested using the \( \chi^2 \)-test. When more than 20% of the cells have an expected count of less than 5, correction for \( \chi^2 \) was conducted using Monte Carlo correction and Fisher’s exact test. Correlation between two quantitative variables were assessed using Spearman’s coefficient.

**Results**

**Clinical characteristics**
The study included 20 female patients, with a mean age of 47.67±12.45 years and a median of 53. The duration of the disease ranged between 2 and 25 years with a mean duration of 10.93±7.66 years.

All the studied patients (100%) received medications with one (5%) patient receiving corticosteroids only, one (5%) patient receiving disease-modifying antirheumatic drugs only, and 18 (90%) patients receiving a combination of these medications (corticosteroids and disease-modifying antirheumatic drugs). No of the studied patients was on biologic therapy. Regarding foot joint examination, the number of tender foot joints ranged between four and 12 joints with a mean of 6.20±2.93 joints. The number of swollen foot joints ranged between two and six joints with a mean of 4.0±1.41 joints.

Table 1 demonstrates demographic data and the studied clinical variables. High disease activity state was present in the studied RA cohort with a mean DAS28 score of 5.89±1.03. Three (15.0%) patients had moderate disease activity and 17 (85.0%) patients had high disease activity. Regarding the HAQ, it ranged between 0.50 and 2.75 with a mean HAQ of 1.89±0.63. Overall, 60% of the patients had moderate functional disability and 35% of patients had severe functional disability. FPI of the studied patients had a mean of 9.93±2.53; 14 (35%) feet were pronated, and 26 (65%) feet were highly pronated.

**Ultrasonographic features of tibialis posterior tendon**
Measurement of TP tendon diameter was recorded in the transverse and longitudinal views at the medial malleolus level, and the longitudinal : transverse ratio was calculated. All data were normally distributed and values are summarized in Table 2. This study results were compared with normal values from the literature [25,26]. Eighteen (45%) feet had thickened transverse diameter. Fifteen (37.5%) feet had thickened longitudinal diameter of the tendon. Thirty-five (87.5%) feet showed increased longitudinal : transverse ratio. Figure 1 shows the thickened longitudinal diameter of the TP tendon in one of the studied patients. Figure 1 show thickened hypoechoic TP tendons (5.8 mm thickness) with anechoic rim (edema along the tendon sheath).

<table>
<thead>
<tr>
<th>Table 1 Demographic and clinical data of the studied patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variables</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>DAS28 score</td>
</tr>
<tr>
<td>HAQ score</td>
</tr>
<tr>
<td>Foot pain VAS (0–100 mm)</td>
</tr>
<tr>
<td>General health VAS (0–100 mm)</td>
</tr>
<tr>
<td>Arthritis VAS (0–100 mm)</td>
</tr>
<tr>
<td>Swollen foot joint count (range 0–14)</td>
</tr>
<tr>
<td>Tender foot joint count (range 0–14)</td>
</tr>
<tr>
<td>ESR</td>
</tr>
<tr>
<td>FPI (range –12–12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2 Ultrasonographic measurements of tibialis posterior tendon diameter in the studied rheumatoid arthritis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tendon diameter</strong></td>
</tr>
<tr>
<td>Transverse diameter (mm)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Longitudinal diameter (mm)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Longitudinal : transverse ratio</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

\( n \), number of feet; mm, millimeter
Regarding the presence of fluid around TP tendon in both views, 19 (47.5%) feet had fluid in the transverse view. Eighteen (45%) feet had fluid longitudinally around the tendon. Fluid was detected only in the retromalleolar region. Figure 2 demonstrates transverse US view of anechoic fluid accumulation around TP tendon in one of the studied patients.

Regarding PDS, eight feet had absent PDS, 10 had mild PDS, and 22 had moderate PDS. The levels of PDS were also recorded at three sites, the greatest level of pathology was recorded at the navicular insertion region, where 18 feet out of 40 scored as moderate, four out of 40 as mild, and 18 out of 40 as absent (Table 3).

Table 3 Distribution of the studied patients regarding power Doppler signal

<table>
<thead>
<tr>
<th>PDS retromalleolar</th>
<th>TP tendon (n=40) [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Mild</td>
<td>9 (22.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>16 (40)</td>
</tr>
<tr>
<td>PDS midway</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Mild</td>
<td>9 (22.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>PDS navicular insertion</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Mild</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Moderate</td>
<td>18 (45)</td>
</tr>
</tbody>
</table>

PDS, power Doppler signal; n, number of feet; TP, tibialis posterior.

Table 4 demonstrates the correlation between FPI and the studied clinical parameters as well as US features of TP tendon. FPI was not significantly correlated with disease duration, BMI, or HAQ. In contrast, there was weak positive correlation between FPI and disease activity (DAS28) ($r=0.3$, $p=0.05$) as well as moderate positive correlation between FPI and transverse diameter thickness of the TP tendon ($r=0.04$, $p=0.01$).
FPI of the studied patients was divided into two groups: pronated and highly pronated groups. The two groups were compared with each other regarding the different clinical and sonographic parameters (Table 5). There was a trend toward longer disease duration (>10 years) in the highly pronated group despite absence of statistical significance. The highly pronated group had significantly higher disease activity (DAS28) \((p=0.03)\). Regarding sonographic features of TP tendon, the highly pronated group had significantly higher transverse diameter thickness and lower longitudinal/transverse diameter ratio. There was a statistically significant relationship between the degree of foot pronation and fluid around TP tendon \((p=0.005)\) as well as PDS around the tendon \((p=0.002)\). The majority of the highly pronated group had fluid around the TP tendon (18 out of 26 feet) and moderate PDS around TP tendon (20 out of 26 feet) (Table 5).

**Discussion**

Up to 80% of RA patients report foot problems during the course of the disease [30]. Pes planovalgus associated with involvement of the TP tendon is common [1]. Treatment requires early diagnosis and intervention to prevent further deformity and disability. Accordingly, if clinical suspicion exists, imaging studies are most useful to determine pathology and help in management [25]. This work assessed TP tendon pathology using high-resolution US and PDS was graded. Relationship of TP tendon pathology to foot posture was studied.

The studied patients had high DAS28 (5.89±1.03) and high visual analog scale for pain indicating high disease activity with increased pain impairing functional activities.

TP tendon often has superficial and deep fibers. It divides into two sets of fibers proximal to the navicular tuberosity. The deep fibers insert directly into the navicular. The superficial fibers cross the navicular and insert into the cuneiforms, cuboid, and metatarsal bones [31–34]. This study showed evidence of abnormal TP tendon thickening in US and increased levels of fluid in the retromalleolar region indicating TP tendon inflammation. The vulnerability of the retromalleolar area to tenosynovitis is related to the presence of fibrocartilage component in this region.

### Table 4 Correlation between foot posture index and the studied parameters (clinical parameters and sonographic features of tibialis posterior tendon)

<table>
<thead>
<tr>
<th>Variables</th>
<th>FPI</th>
<th>(r)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>0.02</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.13</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>ESR</td>
<td>−0.28</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>DAS28</td>
<td>0.3</td>
<td>0.05*</td>
<td></td>
</tr>
<tr>
<td>HAQ</td>
<td>0.06</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>US of TP tendon (transverse diameter thickness)</td>
<td>0.4</td>
<td>0.01*</td>
<td></td>
</tr>
<tr>
<td>US of TP tendon (longitudinal diameter thickness)</td>
<td>−0.12</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>US of TP tendon (longitudinal/transverse ratio)</td>
<td>−0.35</td>
<td>0.03*</td>
<td></td>
</tr>
</tbody>
</table>

DAS28, disease activity score in 28 joints; ESR, erythrocyte sedimentation rate; FPI, foot posture index; HAQ, Health Assessment Questionnaire; \(r\), Spearman’s coefficient; TP, tibialis posterior. \(^*p\leq 0.05\), statistically significant.

### Table 5 Comparison between pronated and highly pronated feet regarding the studied parameters (clinical and sonographic features of tibialis posterior tendon)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pronated feet (6–9) ((n=14))</th>
<th>Highly pronated feet (10–12) ((n=26))</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>11.38±7.82</td>
<td>11.92±7.49</td>
<td>0.79</td>
</tr>
<tr>
<td>BMI</td>
<td>30.67±6.84</td>
<td>32.77±4.95</td>
<td>0.51</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.8±0.72</td>
<td>1.95±0.59</td>
<td>0.91</td>
</tr>
<tr>
<td>ESR</td>
<td>67.63±46.02</td>
<td>41.25±18.24</td>
<td>0.22</td>
</tr>
<tr>
<td>DAS28</td>
<td>6.27±1.54</td>
<td>5.68±0.56</td>
<td>0.03*</td>
</tr>
<tr>
<td>US of TP tendon (longitudinal diameter thickness)</td>
<td>3.47±0.87</td>
<td>3.22±0.9</td>
<td>0.34</td>
</tr>
<tr>
<td>US of TP tendon (transverse diameter thickness)</td>
<td>2.94±1.18</td>
<td>3.85±1.27</td>
<td>0.04*</td>
</tr>
<tr>
<td>US of TP tendon (longitudinal/transverse ratio)</td>
<td>1.35±0.55</td>
<td>0.92±0.34</td>
<td>0.03*</td>
</tr>
<tr>
<td>US-detected fluid around TP tendon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present ((n=18))</td>
<td>14</td>
<td>18</td>
<td>0.005*</td>
</tr>
<tr>
<td>Absent ((n=22))</td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>PDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent ((n=8))</td>
<td>2</td>
<td>6</td>
<td>(\text{MC},p=0.002^*)</td>
</tr>
<tr>
<td>Mild ((n=10))</td>
<td>10</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Moderate ((n=22))</td>
<td>2</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

ESR, erythrocyte sedimentation rate; FPI, foot posture index; HAQ, Health Assessment Questionnaire; MC, Monte Carlo test; \(n\), number of feet; PDS, power Doppler signal; TP, tibialis posterior; US, ultrasound. \(^*p\leq 0.05\), statistically significant.
same as in the tendon insertion. In addition, TP tendon changes direction at this region and is consequently subjected to compressive stress leading to inflammation [35,36]. Regarding PDS around TP tendon, it was found that the majority of patients had PDS and the greatest level of PDS was recorded in navicular insertion region. The navicular insertion of TP is a known site for stress dissipation [33]. A significant portion of the polytrimethylene terephthalate fibers continue to the distal sites of insertion, contacting the fibrocartilage covering the navicular, making the navicular region an area for potential involvement by inflammation in RA patients [33,34]. Accordingly, mild-to-moderate PDS in the navicular insertion region indicates active inflammation.

In agreement with these results, Barn et al. [10] studied 10 patients with moderately active RA and found abnormal thickening and increased levels of fluid in the navicular region. In addition, they reported that seven patients had PDS at the polytrimethylene terephthalate enthesis, indicating active inflammation [8]. In addition, Ward et al. [2] studied 21 patients with RA and reported higher rates of thickened TP tendon approaching the enthesis as well as TP tenosynovial effusion at the enthesis, indicating active inflammation. PDS was detected in more than 15% of RA patients compared with the control participants. They concluded that the TP tendon enthesis was frequently affected in RA patients than in healthy controls or psoriatic arthritis patients [2]. Harman and Tekoeoglu [11] studied 142 inflammatory rheumatic disease patients including 69 RA patients and assessed ankles ultrasonographically. They stated that TP tenosynovitis was significantly more common in the RA group than in the other groups.

In this study, FPI was not significantly related to disease duration; however, the highly pronated feet group had longer disease duration than the pronated group. A larger number of patients are needed to properly assess the relation of disease duration to PPV foot deformity in arthritis patients. Bouysset et al. [37] stated that the PPV deformity increases with increasing disease duration, where patients with long-standing disease duration had highly pronated feet. This could be explained by the fact that RA is a progressive disease; therefore, it is expected that the number and the severity of deformities increase with the duration of the disease especially with poor control and increasing flares. In this study, there was a statistically significant relationship between the FPI and the DAS28. The role of inflammatory mediators cannot be ignored due to the high disease activity in the studied patients. The degree of pronation increases with increasing disease activity. This runs in agreement with several studies [38,39] that reported PPV as a commonly seen deformity in the active stage of RA. In the active stage of RA, there is weakening of the muscles, increased edema, and softening of the ligaments; thus full weight-bearing in this stage may be followed by various deformities, depending on the direction of the influencing forces [40]. The absence of statistically significant relationship between HAQ and the FPI was most probably because FPI indicated the patient current degree of pronation that had already progressed at different points of time and with flares during the course of the disease regardless of the current functional disability status of the patients. There was a statistically significant positive correlation between US transverse diameter thickness of TP tenosynovitis and the FPI. The more the transverse diameter thickness of the TP tendon, the higher the degree of pronation. In addition, detection of PDS and fluid around the TP tendon was more in the highly pronated feet. This suggests that TP tenosynovitis might be a factor contributing to the development of PPV foot deformity. Several authors recognized this condition as a disabling cause of progressive flatfoot deformity [41,42]. Posterior tibialis tendon dysfunction is a primary soft tissue tendinopathy of the posterior tibialis that leads to altered foot biomechanics [43]. Complete tendon rupture is not essential for the development of flatfoot due to the short excursion of the tendon, accordingly less degree of tendon damage may render it ineffective leading to the condition known as TP dysfunction. As the tendon becomes dysfunctional due to inflammatory or mechanical causes, the MLA of the foot collapses causing a relative internal rotation of the tibia and talus. There is eversion of the subtalar joint, which forces the heel into valgus alignment, and abduction at the talonavicular joint [44].

**Conclusion**

This study demonstrated that a higher degree of foot pronation (PPV) in RA patients is associated with US-detected increase in tendon thickness, PDS, and fluid around TP tendon. TP tenosynovitis and high disease activity state might be important factors related to foot impairment and PPV deformity. Accordingly, early management may be needed to reduce TP tendon inflammation and improve foot posture. It is recommended that a larger sample size be studied
for robust conclusions to be drawn and to determine the sensitivity and specificity of different US features in early detection of TP tenosynovitis associated with PPV deformity.

Limitation of the study
The assessment of tarsal tunnel syndrome was beyond the scope of this study and it is recommended to extend this study to include electrodiagnosis of this condition and to examine its incidence to the degree of PPV and US findings.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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23 Redmond A. The foot posture index: easy quantification of standing foot posture: six item version (FPI-6): user guide and manual (online); 2005.


Patellar tendon ultrasonographic properties and lower limb function in rheumatoid arthritis patients
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Aim of work
The aim of this work was to investigate patellar tendon (PT) biomechanical properties in rheumatoid arthritis (RA) patients through changes in ultrasonographic tendon properties and its effect on lower limb function.

Patients and methods
Forty RA patients and 20 healthy participants were included in this study. The physical function was assessed by Health Assessment Questionnaire, the activity of RA by disease activity score 28 and range of motion for all knees by a manual goniometer. RA patients were divided into the following groups: group I comprised patients with low disease activity score 28, who were further subdivided according to the presence of knee flexion deformity into two subgroups (GIA and GIB) and group II patients in the remission stage. Ultrasonography was used for measuring PT elongation and cross-sectional area and quadriceps’ muscle strength was measured. The lower limb function was assessed clinically by 50-foot walk test and smart balance master system through unilateral stance test, step up and over and sit to stand tests.

Results
There was an increased elongation of PT of all RA groups relative to the control group (P=0.001); no significant difference was found in the PT (cross-sectional area). RA patients showed quadriceps’ muscle strength reduction (P=0.001) and delayed walking time of the 50-foot walk test (P=0.05). Unilateral stance test showed increased center of gravity sway velocity during either eye open or eye closed conditions in RA groups and deterioration in all parameters of step up and over and sit to stand tests (P=0.05–0.001). All physical function evaluation of RA patients showed impairment associated with a reduction of PT stiffness and quadriceps’ strength.

Conclusion
Inflammation of the PT and peritendinous tissues in RA alters its biomechanical properties; this impairs RA patients’ physical and lower limb functions.

Keywords: lower limb function and performance, patellar tendon properties, physical function, rheumatoid arthritis

Introduction
Rheumatoid arthritis (RA) is a chronic, systemic, and inflammatory disease that primarily affects the synovial joints and leads to bone and cartilage destruction, as well as shows extra-articular manifestations [1]. Inflammation also affects other musculoskeletal structures including the tendons and their insertions into the bone (entheses) and is accompanied by impaired physical function. But whether this leads to chronic alterations in the biomechanical function of the tendon–muscle complex is unknown [2].

The tendon is responsible for the transmission of contractile forces from muscle to bone, allowing movement to occur [3].

The function of a tendon is determined by its stiffness, that is, its elastic properties, which in turn influence skeletal muscle force output and function. The tendon, however, is not an inextensible tissue, but it deforms in response to the applied load in a manner dependent upon its mechanical properties. When the force of the contracting muscle is transmitted via the tendon, the resulting elongation of the tendon attenuates the impact of the contraction on the connected bone [2].

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Local diffusion of inflammatory cells and molecules from the synovium is thought to be responsible for inflammatory changes seen in and around adjacent tendons in RA. The close proximity of the patellar tendon (PT) to the synovial spaces of the knee joint facilitates its direct exposure to the local inflammatory process [4].

The reduction in PT stiffness in RA is likely due to local and systemic effects of cytokines on the tendon, as proinflammatory cytokines are known to alter tendon structural characteristics in inflammatory arthropathies. The main drivers of the local inflammatory process are tumor necrosis factor-α, interleukin-1 and interleukin-6, which produce proteolytic enzymes such as matrix metalloproteinases that lead to collagen destruction, and the proangiogenic vascular endothelial growth factor, which evokes synovial hyperplasia and infiltration of macrophages and T cells into the synovium. Systemically circulating cytokines could have an additional detrimental effect on the tendon in RA [2,5].

Ultrasound is used to investigate the biomechanical properties of healthy tendons (especially the load-bearing patellar and Achilles tendons) and how they adapt to high-intensity exercise, immobilization, and changes with ageing [6]. Ultrasound is one of the best imaging modalities for assessing tendons due to its high image resolution. When diseased, tendons may become hypoechogenic, with loss of their fine fibrillar pattern, and thicker (diffusely or focally); they have internal Doppler signals and a thickened surrounding tendon sheath, which may exhibit Doppler signals [7].

Tendon properties influence joint stability and the ability to make postural adjustments and thus play a major role to maintain balance and prevent falls [2].

This study aimed to investigate the biomechanical properties of the PT in RA patients and to assess the effect of the changes in tendon ultrasonographic properties (tendon stiffness) on lower limb function and performance.

An approval from the medical ethics committee of Al Azhar University was obtained and conforms to the Helsinki declaration, and all participants included in this study were informed about the study design and a written consent was obtained from them.

Selection of the RA patients was from both sexes; there were 33 (82.5%) female patients and seven (17.5%) male patients. Their ages ranged between 29 and 64 years with a mean age of 47 years; their disease duration ranged from 3 to 23 years with a mean duration of 11 ±6.63 years.

The activity of RA was assessed using the 28-joint disease activity score (DAS-28) and pain was evaluated using the visual analogue pain scale.

Patients were included in this study if their disease duration was at least 3 years and if they had a stable disease activity (no flare or change in medication for the past 3 months) to ensure that all the patients were able to stand on the balance platform and to withstand posturographic evaluation with tolerable pain. They were excluded if they had any other autoimmune or neurological diseases, were under high-dose steroid therapy (>10 mg prednisolone/day), had a recent knee steroid injection, had a joint replacement or current severe knee pain or effusion.

The patients were divided according to their DAS-28 [8] into two groups: group I comprised patients in a stage of low disease activity; there were a total of 20 patients (40 knees). Group II comprised patients in a stage of remission; there were a total of 20 patients (40 knees). Group I patients were subdivided according to the presence of knee flexion deformity into GIA, which comprised nine patients with knee flexion deformity, and GIB, which comprised 11 patients without knee flexion deformity.

All participants were subjected to the following assessments:

(1) Full history taking.
(2) Clinical examination and routine laboratory investigation.
(3) Health Assessment Questionnaire (HAQ), using its final version. It includes 20 questions in eight subdimensions: dressing and grooming, getting up, eating, walking, hygiene, reach, grip, and common daily activities (0–1 represent mild to moderate impairment, 1–2 moderate to severe impairment, and 2–3 severe to very severe impairment) [9].
(4) Biomechanical properties of the PT have been evaluated by the following tests:
(a) Ultrasonography for PT measurements: PT length, elongation and cross-sectional area (CSA) were assessed using Xario 200, Toshiba ultrasound machine (Toshiba, Toshiba medical systems corporation, Tochigi, Japan), using multifrequency linear probe with frequency 11 Mega Hertz in B-mode. PT length is the distance between the inferior pole of the patella and the superior aspect of the tibial tuberosity visualized on sagittal plane. Participants sat upright; the knee joint angle was fixed at 90 from full leg extension and the hip angle at 90. After a set protocol of warm-up contractions, participants performed maximal voluntary isometric knee extension contractions, building up to maximum force [10]. Ultrasound images were recorded at full knee extension and with the knee joint at 90°. The CSA of PT was measured as three ultrasound images taken in the axial plane at 25, 50, and 75% of the PT length. The mean CSA was calculated using the following three measurements.
(b) Quadriceps muscle power by manual push-pull dynamometry expressed in kilograms.
(5) Physical function performance of the lower limb was assessed by the following tests:
(a) Clinically by estimating walking time by 50-foot walk test (FWT). The protocol has been described by Gill and McBurney [11] as the 50 FWT that has been completed by walking 25 feet, turning around 180° and walking 25 feet back to the starting position. Participants were advised to 'go as fast as you can safely walk.' The time taken was assessed with a hand-held stopwatch and recorded in seconds.
(b) Computerized dynamic posturography (Balance Master System, version 8), Neurocom International Incorporation manual [12]: Balance Master System compares test results to normative data (on the software of the apparatus) relative to corresponding age, sex, and height.
(i) Unilateral stance test (UST): The US quantifies postural sway velocity with the patient standing on either the right or left foot on the force plate, with eyes open and with eyes closed. There were three trials for each condition; the length of each trial was ten seconds. The center of gravity (COG) sway velocity scores indicate how well the patient accomplished this objective. Small scores reflect little movement and are good.
(ii) Step up and over (SUO) test: the patient is instructed to step up onto a curb using a 20 cm wooden step placed in the center of the platform; on command, the patient will step with one foot, swing the other foot over the curb while lifting the body through an erect standing position as quickly as possible, and then lower the body weight to land the swing leg as gently as possible. The SUO measures, for each leg, the strength of the rise (lift up index), which was recorded by the percentage of body weight exerted to lift the leading leg to the wooden step, the movement time, and the impact of the swing leg landing (impact index), which was expressed as the percentage of body weight used to step down onto the force plate.
(iii) Sit to stand (STS) test: the participants were instructed to stand up as quickly as possible, but they were not allowed to use arms or hands to push off their legs or the seat surface. They were also instructed to stand as still as possible for 5 s following the STS movement as part of the COG sway measurement. The STS procedure was repeated three times.

The measured parameters were weight transfer time, rising index, and sway velocity during the rising phase. Weight transfer time expressed in seconds is the time required to voluntarily shift COG forward, beginning in the seated position and ending with full weight bearing on the feet. Rising index is the amount of force exerted by the legs during the rising phase. The force is expressed as a percentage of the patient's body weight. COG sway velocity documents control of the COG over the base of support during the rising phase and for 5 s thereafter. Sway is expressed in degrees per second.

Statistical analysis
Data were analyzed using statistical program for the social science (IBM Inc., NY city, NY, USA), version 20.0. Quantitative data were expressed as mean±SD. Qualitative data were expressed as frequency and percentage. The following tests were carried out:
(1) Independent samples t test of significance was used when comparing between two means.
(2) χ² test of significance was used in order to compare proportions between two qualitative parameters.
Pearson’s correlation coefficient (r) test was used for correlating data.

P value less than 0.05 was considered significant.

Results
The present study was conducted on 40 RA patients (80 knees), and 20 healthy participants (40 knees) as a control group. The patients’ characteristics are presented in Table 1.

The patients were divided according to disease activity score DAS-28 into two groups.

Group I (in a stage of low disease activity)
There were 20 patients (40 knees), and they were subdivided into the following subgroups: Subgroup IA: This subgroup comprised nine patients (18 knees) with knee flexion deformity, seven female patients and two male patients, with ages ranging between 45 and 57 years with a mean age of 52.44 ±3.54 years; their disease duration ranged from 5 to 23 years with a mean duration of 13.44±5.85 years, and their flexion deformity ranged from 10 to 30° with mean flexion deformity of 15°.

Subgroup IB: this subgroup comprised 11 patients (22 knees) without knee flexion deformity, nine female patients and two male patients, with their ages ranging between 32 and 64 years with a mean age of 47.64±10.25 years; their disease duration ranged from 3 to 22 years with a mean duration of 8.8±6 years.

Group II (in a stage of remission)
There were 20 patients (40 knees) in this group, all without knee flexion deformity; there were 17 female patients and three male patients, with their ages ranging between 29 and 56 years with a mean age of 43.15±7.86 years, matching in age with RA patients. Table 2 shows their PT properties, quadriceps muscle power and 50 FWT results. The control participants’ PT elongation was considered as the standard for evaluation; the mean was 2.81±0.41 mm (100%).

On comparing the biomechanical properties of the PT between patient groups and the control group, with regard to subgroup IA, there was increased elongation of PT by 31.3%, with a mean of 4.09 ±0.69 mm, which indicates reduction of PT stiffness, with high significant difference between subgroup IA and the control group (P<0.001). However, subgroup IB showed increased elongation of PT by 20.9%, with a mean of 3.54±0.57 mm, with a significant difference between subgroup IB and the control group. Moreover, there was increased elongation of PT in group II by 15.66%, with a mean of 3.32±0.49 mm, with a significant difference between group II and the control group (Figs 1–3).

As regards PT CSA, there was no significant difference between the RA patient groups and the control group (P>0.05). The mean CSA of the control group was 90.62±3.00 mm², subgroup IA was 90.28±3.31 mm², while the mean of subgroup IB was 89.70±5.78 mm², and the mean of group II was 90.11±5.52 mm².

### Table 1 Rheumatoid arthritis patients’ characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>RA patients (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [range (mean)] (years)</td>
<td>29–64 (47±10.01)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>3–23 (11±6.63)</td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Female patients</td>
<td>25 (62.5)</td>
</tr>
<tr>
<td>Male patients</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>RF positive [n (%)]</td>
<td>25 (62.5)</td>
</tr>
<tr>
<td>Anti-CCP positive [n (%)]</td>
<td>28 (70)</td>
</tr>
<tr>
<td>ESR [range (mean)] (mm/h)</td>
<td>11–45 (28.38±10.34)</td>
</tr>
<tr>
<td>Medical treatment (last 6 months) [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>23 (57.5)</td>
</tr>
<tr>
<td>Antimalarial</td>
<td>37 (92.5)</td>
</tr>
<tr>
<td>Leflunamide</td>
<td>21 (52.5)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>40 (100)</td>
</tr>
<tr>
<td>Pain according to VAS [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Mild (&lt;OR=5)</td>
<td>21 (52.5)</td>
</tr>
<tr>
<td>Moderate (6–7)</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>DAS-28 [range (mean)]</td>
<td>1.5–3.19 (2.37±0.52)</td>
</tr>
</tbody>
</table>

DAS-28, 28-joint disease activity score; CCP, cyclic citrullinated peptide; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; VAS, visual analogue scale.

### Table 2 Quadriceps’ muscle strength, patellar tendon elongation, patellar tendon cross-sectional area, and 50-foot walk test of the control participants

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadriceps strength (kg)</td>
<td>32</td>
<td>38</td>
<td>35.40</td>
</tr>
<tr>
<td>PT elongation (mm)</td>
<td>1.8</td>
<td>3.6</td>
<td>2.81</td>
</tr>
<tr>
<td>PT CSA (mm²)</td>
<td>84.1</td>
<td>99.8</td>
<td>90.62</td>
</tr>
<tr>
<td>50 FWT (s)</td>
<td>9</td>
<td>18.2</td>
<td>13.83</td>
</tr>
</tbody>
</table>

50 FWT, 50-foot walk test; CSA, cross-sectional area; PT, patellar tendon.
The HAQ of subgroup IA ranged from 1 to 1.9, with a mean of 1.31±0.30, which is severely impaired, while HAQ of subgroup IB ranged from 0.3 to 1), with a mean of 0.61±0.27, which is impaired, and, for group II, it ranged from 0 to 0.9, with a mean of 0.36±0.3, which is impaired (Table 3).

On comparing the quadriceps muscle strength between the RA patient groups and the control group, all patient groups showed a reduction of quadriceps’ muscle strength with a significant to highly significant difference between them and the control group (Fig. 4).

Concerning the physical performance of the lower limbs, all patient groups showed a delay in walking time in the 50 FWT time by 54.6% for subgroup IA, 46.5% for subgroup IB and 40.9% for group II, as compared with the control group, with highly significant difference between all patient groups and the control group (Fig. 4).

Posturographic evaluation, as a part of lower limb functional evaluation showed that, with regard to
the UST, all patient groups showed increased COG sway velocity in right eye open (EO), right eye closed (EC), left EO, and left EC conditions in comparison with the healthy control group, with significant to highly significant difference between all the patient groups and the control group (Table 4).

Subgroup IA patients showed more increase of sway velocity by 74.2% and 78.3% with regard to right EO and left EO conditions, respectively, while it increased by 51.2 and (50.9%) with regard to right EC and left EC, respectively, due to improper alignment of the lower limb joints and lag of knee extension (Table 4).

As regards the SUO test, the mean lift up index of subgroup IA was 24.31±2.19%, and decreased by 36.8% relative to the control group; the mean for subgroup IB was 32.26±7.64%, and it decreased by 23.4% relative to the control group; the mean for group II was 32.90±6.85%, and it decreased by 23.2% relative to the control group.

While the mean movement time for subgroup IA was 3.71±0.71 s and increased relative to the control group by 56.9%, the mean for subgroup IB was 1.97±0.49 s, and it increased relative to the standard evaluation by 29.3%; the mean for group II was 1.88±0.62 s, and it increased by 26.6% relative to the control group.
The mean impact index of subgroup IA was 32.63 ±5.73%, and it decreased relative to the control group by 32.6%; the mean for subgroup IB was 32.63±5.73%, and it decreased relative to the standard evaluation by 32.6%; the mean for group II was 42.44±9.47%, and it decreased relative to the control. Significant to highly significant difference was found between all patient groups and the control group in all of the evaluated parameters of the SUO test (Table 4 and Fig. 5).

Concerning the STS test, subgroup IA showed prolongation of the time to transfer weight, with a mean of 1.96±0.29 s, and it increased by 81.1%, relative to the control group; for subgroup IB, it was 0.67
±0.45 s, and it increased by 44.8% relative to the controls; for group II, it was 0.50±0.50 s, and the time increased relative to the controls by 26%.

The mean rising index of subgroup IA was 12.98 ±4.13%, and it decreased by 56% relative to the controls; for subgroup IB, it was 13.14±4.24%, and it decreased by 55.5% relative to the control group; for group II it was 14.28±3.91%, and it decreased by 51.6% relative to the control group.

The mean COG sway velocity of subgroup A was 7.97±1.39°/s, and it increased by 53.2% in comparison with the control; for subgroup IB, it was 5.56±0.83°/s, and it increased by 31.8% in comparison with the controls; for group II, it was 5.47±0.56°/s, and it increased relative to the standard evaluation by 32.9% (Table 4). A linear positive correlation was found between PT elongation and 50 FWT, STS test parameters (weight transfer, COG sway), movement time of the SUO test, and UST parameters (sway velocity during EO and EC conditions) in RA patients.

A linear negative correlation was found between PT elongation and lift up index and impact index parameters of the SUO test.

A linear negative correlation was found between quadriceps’ muscle strength and 50 FWT, parameters of the STS test (weight transfer and COG sway), parameters of the UST (sway velocity during EO and EC conditions), and movement time of the SUO test in RA patients. While a linear positive correlation was found between quadriceps’ muscle power and SUO test parameters (lift up and impact index) and STS test parameter (rising index) in RA.

**Discussion**

Tendons are extensible structures that reversibly deform when a mechanical load is applied [10]. Tendon properties influence motor control, joint stability, and the ability to make postural adjustments and, consequently, play a major role in maintaining balance and preventing falls [2,6,13]. The mechanical properties of tendons are essential for proprioception and for the reflex responses involved in the rapid adjustment of muscle tension to positional changes, as well as the stored elastic strain energy, which is key to efficient locomotion [6].

This can be explained by the fact that the reduced stiffness of the tendon reduces muscle fascicle length changes in response to passive joint movements and thereby impairs recognition of small movements by the muscle spindle [14].

The extent of elongation of a tendon to loading, that is, the tendon stiffness influences the performance of the attached muscle, and thereby determines the magnitude and speed with which the force is transmitted from the muscle to the bone. Therefore, stiffer tendons result in increased and faster force production, whereas the opposite effect is seen in more compliant tendons, as increased elongation of the tendon requires further shortening of the muscle fibers, causing electromechanical delay [3]. This reduction of the tendon stiffness was correlated with decreased neuromuscular performance, either static as postural stability or dynamic as walking [15].

RA is a chronic autoimmune arthritis characterized by joint inflammation and progressive joint destruction and is accompanied by impaired physical function. Inflammation also affects other musculoskeletal structures including tendons; this leads to chronic alterations in the biomechanical function of the tendon–muscle complex [2].

The aim of this study was to investigate the biomechanical properties of the human PT in RA patients and, consequently, to assess the effect of the changes in PT properties (tendon stiffness) on lower limb function and performance, as compared with healthy age-matched and sex-matched control participants, by using ultrasonography to determine PT elongation and CSA, and measure knee extensor strength. However, the assessment of lower limb functional performance was carried out clinically by 50 FWT and by using smart balance master system, through UST, STS, and SUO tests.

With regard to PT elongation, all the RA patients (80 knees) showed increased PT elongation more than the control group. This increased PT elongation of all groups of RA patients indicates a reduction of PT stiffness relative to the control group. In a previous research, they studied the changes of Achilles tendon stiffness in patients with Achilles tendinopathy; they found that tendinopathy weakens the mechanical and material properties of the tendon. Tendinopathic tendons had more increased elongation and lower tendon stiffness relative to the control group [16].

The reduction of tendon stiffness in RA patients is the result of destruction of the tendon and the tenosynovium by proinflammatory cytokines, supported by a research study that the role of proinflammatory cytokines,
VEGF and MMPS on the destruction of tendons of RA, by cultured specimens of RA synovium (joint synovium, invasive tenosynovium, and encapsulated tenosynovium) in vitro, they found a high level of proinflammatory cytokines and proteolytic enzymes in the tenosynovium of RA similar to joint synovium, and that the proteolytic enzymes are produced in higher amounts by invasive tenosynovium compared with encapsulating tenosynovium, which explained the worse prognosis and increased rupture rate associated with invasive tenosynovitis in RA [5]. Another study added that RA tenosynovitis and joint synovitis exhibit indistinguishable histological features, including hyperplasia of the synovial lining layers and infiltration of leukocytes, largely CD4+ T cells and CD68+ macrophages [17].

A previous study found that all RA patients in their study had stable low DAS-28, and showed increased PT elongation at maximal voluntary isometric knee extension contractions, which indicates the reduction of PT stiffness relative to the control group in agreement with our results [2]. In another study, despite the stabilization of disease activity, there was no recovery of the PT biomechanics, wherein tendon stiffness is reduced, although there was a resolution of disease activity, which is likely due to local and systemic effects of cytokines on the tendon [18].

The current study showed an insignificant difference in PT CSA between the RA patient groups and the control group. This is in agreement with previous studies, which found that PT CSA of RA patients was 91.4±4.5 mm², and, of the healthy control group, it was 91.3±2.6 mm², with no significant difference between the two groups [2,18]. When they compared CSA of PT between ankylosing spondylitis patients and RA patients, they reported increased PT CSA of ankylosing patients more than that of RA patients, and they explained that it was due to the different pathology of both diseases, which was characteristic enthesal inflammatory changes of perienthesal swelling and edema and bone marrow edema associated with knee synovitis in spondyloarthropathies. These changes are not seen in RA [2].

A former research studied the relation between the mechanical properties of PT and quadriceps muscle strength in humans; they found that there is a positive correlation between both of them [19].

With regard to quadriceps muscle strength, our results showed that there was a reduction of quadriceps muscle strength of all RA patient groups relative to the control group. Group IA showed the greatest reduction of strength. These results were supported by two studies, which stated that RA quadriceps muscle strength was weaker than that of healthy participants. They suggested that there is abnormal afferent information from articular mechanoreceptors, occurring as a result of joint damage, effusion, pain, and/or psychological factors, which decreases quadriceps motor neuron excitability via neurophysiological pathway in the spinal cord and supraspinal centers, and that this impairs voluntary activation, which is manifested as quadriceps’ weakness [20,21].

A prior research work studied the physiological properties of the skeletal muscle in 23 stable RA patients, and they concluded that physiological muscle properties were preserved in patients with stable RA [22].

The current study assessed the functional performance of the lower limb in RA patients by the 50 FWT, UST, SUO test, and STS test.

On performing the 50 FWT, there was a highly significant difference between RA patient groups and the control group. Group IA showed the worst performance in 50 FWT than those with low disease activity or remission without knee flexion. GIA showed more delay in walking time, as flexion contracture has an adverse effect on function. Flexed knees require a considerable expenditure of energy by the quadriceps, with a consequent increase in the forces across the patellofemoral and tibiofemoral joints [23].

Our results are supported by an earlier study. It explained this delayed walking time by pain, stiffness, muscle weakness, and fear of falling in RA patients. This requires a great cognitive effort in these patients to maintain stability [24].

Our results are supported by several former studies [25–27] that reported that RA patients walk slower than healthy controls. Another study explained that the impairment of physical functional performance in 50 FWT was associated with quadriceps weakness and proprioception deficits in RA patients [20].

A prior research investigated the properties of skeletal muscles in RA patients and its effect on the physical performance of the patients; they found that there is a delay in walk time in RA patients relative to the control due to muscle weakness [22]. Later, they continued
their studies on muscle–tendon complex, especially PT, and they concluded that alterations of tendon properties play a role in this delay of walking time in RA patients [2,18].

We also found a negative correlation between the walking time of our RA patients and their quadriceps muscle strength and PT stiffness. This agrees with a former study that found that the knee extensor strength is negatively correlated with walking time [28].

UST (US-EO and US-EC) results in our study showed that there was an evident difference as regards COG sway in both EO and EC conditions for RA patient groups relative to the controls of the same age and sex. The presence of postural sway at US-EO reveals instability due to lower limb joints, tendon properties, and muscle weakness affection in RA. Moreover, the increased sway during US-EC denotes altered proprioception, which cannot be compensated when eyes are closed. Our results agreed with Rome et al. [24] who studied static postural stability in RA patients and reported that RA patients might be markedly dependent upon visual information to maintain anterior–posterior stability, as stability was compromised with visual deprivation.

Several studies documented that there was a poorer performance of RA patients for this task in comparison with healthy controls, which was linked to the changes of tendon–muscle complex mechanical properties [3,18,22]. Other authors documented a relationship between compromised postural stability and tendon stiffness: the muscle strength and the mechanical properties of the tendon had a significant association with postural sway in the UST [6].

RA patients in the current study showed significant deterioration in the lift up index, movement time, and impact index of the SUO test in comparison with the normal standard. The lift up and impact indices were more obviously reduced, and movement time was more prolonged in GIA; this is possibly secondary to joint movement delay and muscles’ inco-ordination of the lower extremity, which affects joint trajectory of the lower limbs, in addition to the reduction of PT stiffness.

In the STS test, our RA patients showed significant deterioration in weight transfer, rising index and sway velocity of COG in relation to the normal standard, with more affection of GIA. This can be attributed to the presence of pain and fear of falling secondary to the adverse effect of RA on muscle–tendon mechanical properties and affection of proprioception. A former study reported that the ambulatory impairments present in RA patients force them to modify activities due to fear of falling, resulting in increased time demands to perform STS and foot up and go tests [34]. Another study added that pain increased the weight transfer time of the STS, as patients transfer from a sitting to a standing position in a more cautious manner. Moreover, deficits in the lower limb proprioception and muscle strength of RA patients play a role in balance impairment [29].

RA patients with low disease activity in this study showed more tendon elongation, and they were the worst with regard to the quadriceps muscle strength; they showed the worst performance in all lower limb functional performance tests. This is in agreement with a previous study, which reported that disease activity and functional disability (HAQ) in patients with RA, correlated with worse performance in STS and foot up and go tests, due to pain during disease activity [30]. Other authors explained the reduction of objective physical function of RA patients by using STS and foot up and go tests in relation to the controls by RA effect on PT properties [2]. Thus, treatment of RA is directed to suppressing inflammation, with the aim of eliminating synovitis and establishing a state of remission. Remission is regarded as the ideal therapeutic target for patients with RA, because further joint damage and disability should be prevented and function and quality of life maintained [31].

In this study, RA patients with flexion deformity (GIA) showed the worst performance in all physical function tests, which is supported by a prior study that documented a relationship between the range of motion and the disability and found that the more the restriction of range of motion the more the disability [32]. In addition, articular damage may reduce quadriceps motoneuron excitability, which decreases voluntary quadriceps activation, thus contributing to quadriceps weakness, and diminishes proprioceptive acuity. The arthrogenic impairment in quadriceps sensorimotor function and decreased postural stability were associated with reduced functional performance [33].

**Conclusion**

As a consequence of the inflammation of the PT and peritendinous tissues in RA patients, affection of the biomechanical properties of the tendon becomes a common pathological lesion in patients with RA.
The present study revealed that the adverse changes in PT mechanical properties in RA patients may contribute to the impaired physical function. Knee flexion deformity also impairs functional performance in RA.

RA disease activity influences PT stiffness, which reflects the systemic effect of RA on the PT, and is related to worse functional performance.

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**Conflicts of interest**
There are no conflicts of interest.

**References**

Combined (physical and medical treatment) therapy versus physical treatment alone and medical treatment alone in the management of chronic pelvic inflammatory disease

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Context
Pelvic inflammatory disease (PID) is the inflammation of the upper genital tract involving the fallopian tubes as well as the ovaries. Symptoms of PID are fever, cervical motion tenderness, lower abdominal pain, new or different discharge, painful intercourse, uterine and adnexal tenderness, and irregular menstruation.

Aim
The aim was to determine the therapeutic efficacy of combined shortwave diathermy and medical treatment in the management of chronic PID in comparison to either therapy alone.

Materials and methods
Sixty participants were recruited and diagnosed as chronic PID for more than 6 months by history, clinical examination, cervical swab, and ultrasonography. They were divided into three groups:

Statistical analysis
Descriptive and analytic study by SPSS version 16 on IBM compatible computer.

Results
There was a statistically highly significant clinical improvement regarding itching, discharge and pain relief, laboratory improvement regarding the number of pus cells in cervical swab, and radiological improvement regarding US parameters in the first group of patients with PID compared with the baseline and compared with other groups.

Conclusion
The greatest therapeutic efficacy can be obtained from combined physical and medical treatment compared with each line alone in the treatment of chronic PID.

Keywords:
combined therapy, medical treatment, pelvic inflammatory disease, physical therapy, shortwave diathermy, visual analog scale

Introduction
Pelvic inflammatory disease (PID) and upper genital tract infection describe inflammatory changes in the upper female genital tract including any of the following combinations: endometritis, salpingitis, tubo-ovarian abscess, and peritonitis in the small pelvis and in most cases the infection is ascending. The spectrum ranges from subclinical, asymptomatic infection to severe, life-threatening illness [1–4].

Symptoms of PID include fever, cervical motion tenderness, lower abdominal pain, new or different discharge, painful intercourse, uterine and adnexal tenderness, or irregular menstruation [2]. Tubal sterility, ectopic pregnancy, and tubo-ovarian abscess are the long-term sequel [4]. Chronic PID refers to both residue of acute and subacute recurrence of a previous infection [4,5].

The aim of PID management is to alleviate pain and systemic malaise associated with infection, to achieve microbiological cure, to prevent the development of permanent tubal damage with associated sequel such as chronic pelvic pain, ectopic pregnancy, and infertility and to prevent the spread of infection to other parts [4]. It is widely claimed that shortwave diathermy (SWD) can be used to reduce pain and swelling, accelerates the anti-inflammatory process, and promotes healing in tissues with chronic inflammation. The SWD is high-frequency electromagnetic waves (current is of high alternating frequency) that do not stimulate motor or sensory nerves; it is a form of radiofrequency radiation, operating at a frequency of 27.12 MHz, used therapeutically by physiotherapists [4–6].

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Application of SWD to the involved tissues may increase vascular circulation which directly results in vascular dilatation, increase in pain threshold, and a decrease in pain and swelling. Such vascular improvement also encourages resolution of the inflammatory processes by increasing nutrition, oxygen supply, and by removing metabolic and waste products and in turn promotes natural resistance to infection [4,7].

For women with PID of mild to moderate severity, parenteral and oral therapies appear to be effective [8]. Typical regimens include second-generation cephamycin plus macrolides and lincosamide plus aminoglycosides.

**Aim**

The aim was to compare the therapeutic efficacy of combined (medical and physical treatment) therapy with medical treatment only and physical treatment only for the management of chronic PID.

**Participants and methods**

**Participants**

The present study included 60 participants diagnosed as chronic PID and met the inclusion criteria referred from the gynecology clinics to Physical Medicine, Rheumatology and Rehabilitation Department, Menofiya University Hospitals.

**Inclusion criteria**

Patients diagnosed as PID according to CDC diagnostic criteria for PID [9] for more than 6 months by history, clinical, and laboratory (microbiological) examination indicating the presence of pus cells.

1. CDC Diagnostic Criteria for the Diagnosis of PID [9].
2. Minimal criteria*.
3. Lower abdominal tenderness, uterine/adnexal tenderness, cervical motion tenderness.
4. Additional criteria.
5. Oral temperature greater than 38.3°C (101°F).
6. Abnormal cervical or vaginal mucopurulent discharge.
7. Presence of white blood cells (WBCs) on saline microscopy of vaginal secretions.
8. Elevated erythrocyte sedimentation rate.
9. Elevated C-reactive protein level.
10. Laboratory documentation of cervical infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.
11. Definitive criteria.
13. Transvaginal sonography or MRI techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex.
14. Laparoscopic abnormalities consistent with PID.
15. Practically gynecologists diagnoses patients with PID regarding all minimal criteria or one more of additional criteria.

**Exclusion criteria**

Those with acute PID and other acute genital infections, intrauterine device/implants, cardiac pacemaker, active tuberculosis, tumor, pregnancy, skin sensation defect, severely ill patients, intolerance to oral antibiotics, analgesics, and electromagnetic therapy.

**Methods**

Informed consent was written by patients who participate in the present study.

1. Full clinical examination which includes general and local examination.
2. General examination: pulse, blood pressure, temperature, respiratory rate, chest, abdomen, etc.

**Local examination**

1. Bimanual examination to ascertain the criteria of PID as cervical motion tenderness, adnexal tenderness, and uterine tenderness. Cusco speculum was then introduced to visualize the cervix and end cervical swab was obtained and sent for bacteriological examination. This was done by a gynecologist who is a member of our team.
2. Ask the patients about symptoms of PID as: pelvic pain, itching, and discharge.
3. Pretreatment pain index assessment through the visual analog scale (VAS) was used for the assessment of pelvic pain [8,10]. It is a scale, using a 10-cm line divided into 10 equal sections, with 0 representing ‘no pain’ and 10 representing ‘unbearable pain’. Each participant was asked to indicate on the scale the level of pain in their lower abdominal and pelvic region.
4. Diagnostic ultrasound: was performed before and after the treatment to detect any pathology including adnexal mass, dilated tube, and fluid in the pouch of Douglass and the improvement of the case after treatment.

**Laboratory measures**

1. Pretreatment (endocervical swab). During the pelvic examination, specimens were obtained from the endocervix and the vagina (posterior
fornix and sidewall) and placed in separate tubes of normal saline. Each specimen was examined for the number of WBCs.

(2) Erythrocyte sedimentation rate, C-reactive protein.

The patients were divided into three groups (20 patients in each group) according to the following:

(1) First group (group 1): received both medical treatment + physical treatment.
(2) Second group (group 2): received only physical treatment.
(3) Third group (group 3): received only medical treatment.

Patients for SWD groups (group 1 and group 2) were screened for all the contraindications to SWD through the past medical and family history. A thermal skin sensation test was carried out.

**Physical treatment procedure**

A continuous SWD current was generated by the shortwave diathermy machine (CURAPULS 970; Enraf-Nonius, The Netherlands) adopting the modified crossfire technique as described by Lamina et al. [5]. This involved moving electrodes to a position at right angles to their previous position halfway through treatment. In this way, half the treatment was given anteroposteriorly through the pelvis with the patients in supine lying position and second half with the patients in the side lying positions with their legs curled up and the electrodes over the pelvic outlets and the lumbosacral area of the spine. An intensity that generated moderate pleasant sensation of warmth (dose III) in the Kloth definitions of dosage for SWD was used [11].

Treatment was given every alternative day for a total of 15 exposures treatment sessions. The treatment duration was 20 min split into two sessions of 10 min per session in the crossfire positions [12].

**Medical treatment**

Antibiotics: oral doxycycline 100 mg twice daily and metronidazole 500 mg twice daily for 14 days according to the 2015 Sexually Transmitted Disease treatment guidelines [9].

**Post-treatment procedure**

At the end of the 14-day treatment duration for the medical group and 5-week treatment duration for physical and combined groups all participants were assessed for:

(1) Post-treatment pain score (VAS) using the same pretreatment procedure [8, 10].
(2) Post-treatment laboratory (end cervical swab): each specimen was examined for the number of WBCs compared with previous results before treatment.
(3) Post-treatment US: to detect the improvement of previous pathology.
(4) Post-treatment symptoms of PID regarding pain, itching, and discharge.

The data collected were tabulated and analyzed by SPSS (the statistical package for the social sciences software) statistical package version 16 on IBM compatible computer (IBM Corporation, and is one of the brands under IBM Software Group’s Business Analytics Portfolio, Chicago, USA). Two types of statistics were done: descriptive statistics included percentage, mean, and SD and analytical statistics: Student’s t-test, $\chi^2$-test. P value nonsignificant if $P$ greater than 0.05, significant difference if $P$ less than 0.05, and highly significant difference if $P$ less than 0.001 [13].

**Results**

The study group was homogenous and matched as there was no significant difference among patients of the study groups regarding age, Body Mass Index (BMI) and disease duration as shown in Table 1 and Fig. 1.

There was highly statistical significant clinical improvement regarding itching, discharge and pain relief in the first group of patients with PID compared to the baseline and compared to other groups as illustrated in Table 2 and Fig. 2.

There was highly statistical significant pain reduction regarding VAS in the first and second groups compared to the baseline and compared to the third group with more improvement of the first group and as shown in Table 3 and Fig. 3.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study groups (mean±SD)</th>
<th>F test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (N=20)</td>
<td></td>
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<tr>
<td></td>
<td>Group 2 (N=20)</td>
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<tr>
<td></td>
<td>Group 3 (N=20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>39.6±6.2</td>
<td>33.9±5.8</td>
<td>33.1±6.9</td>
</tr>
<tr>
<td>Disease duration</td>
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<td>2.95±2.2</td>
<td>2.76±1.9</td>
</tr>
<tr>
<td>BMI</td>
<td>23.52±3.2</td>
<td>25.96±3.7</td>
<td>24.22±3.20</td>
</tr>
</tbody>
</table>

This table shows insignificant differences regarding age, disease duration, and BMI among the studied groups.
There was highly statistical significant laboratory improvement regarding reduction of number of pus cells in the cervical swab in the first group of patients compared to the baseline, and to other groups as in Table 4 and Fig. 4.

There was highly statistical significant radiological improvement regarding reduction of fluid in Douglas pouch as a parameter of US study in the first group of patients compared to the baseline, and to other groups as in Table 5 and Fig. 5.
The main purpose of this study was to assess the therapeutic efficacy of combined SWD and medical treatment in the management of chronic PID in comparison to either therapy alone.

The statistically highly significant improvement of clinical symptoms regarding itching, discharge, and pain relief was observed in the first group of patients with PID who received a combined medical and physical treatment therapy compared with other groups and compared with the baseline.

This comes in agreement with Lamina et al. [5] who reported a statistically significant improvement of pain and inflammatory signs and symptoms in the group of patients who received combined antibiotics and SWD compared with baseline and compared with other groups.
Our study observed a statistically highly significant reduction of pelvic pain regarding VAS in the first (combined therapy) and second (physical treatment only) groups of patients compared with the baseline and compared with the third group with more improvement of the first group.

Figure 3

Graph 3 shows highly significant difference regarding visual analog scale before and after treatment in group 1 and insignificant differences in the two other groups.

Figure 4

Graph 4 shows highly significant difference regarding the number of pus cells in cervical swab before and after treatment in group 1 with insignificant differences in the two other groups.
This points to the synergistic effects of the combined therapy in reduction of pain and improvement of inflammatory symptoms which is explained by the therapeutic benefits of medical treatment in attacking the causative microorganisms and the physiological effects of physical treatment (SWD) regarding improvement of circulation with subsequent delivery of oxygen and removal of the metabolic waste products of the involved organs and regarding the sedative and comfortable effects of deep heat radiation to those tissues.

In accordance with our results Sonali et al. [14] reported the superiority of SWD over medical treatment (antibiotics and analgesics) in the management of chronic PID and also Balogun and Okonofua [15] reported a significant improvement of pain regarding VAS in a group of patients with PID who received SWD compared with those who received medical treatment.

Evseeva et al. [4] also reported that SWD produced marked and long-term positive effects (≥18 months) on pain relief compared with medical treatment.

In the same way, the Lamina et al. [5] study reported significant effects of combined medical and physical treatment over medical treatment (analgesic and antibiotic) in pain responses and resolution of inflammation in PID patients.

Further evaluation of patients of the study groups regarding our aim of study we reported a statistically highly significant reduction in the number of pus cells in the cervical swab in the first group of patients compared with other groups and compared with the baseline.

This explains the greatest therapeutic value of combined medical (regarding its pharmacologic effects on microorganisms and its antiseptic properties) and physical treatment (regarding its anti-inflammatory and vascular enhancement effects) in reducing the number of pus cells and minimizing inflammatory cells as WBCs compared with physical therapy alone without the antiseptic effects of medical treatment and medical therapy alone without the vascular enhancement effects of physical treatment.

Lamina et al. [5] reported similar results in their study as they observed a significant reduction in the number of pus cells number after treatment with combined physical and medical treatment of chronic PID compared with baseline and over other groups.

Finally as regards radiological assessment there was a highly statistically significant improvement and reduction of fluid in the pouch of Douglas as a parameter of US study in the first group of patients.
compared with other groups and compared with the baseline, owing to the combined antiseptic, anti-inflammatory, and vascular enhancement effects of physical and medical treatment which is in agreement with Lamina et al. [5] as their study supported the anti-inflammatory effects of combined medical and physical treatment in cases of chronic PID.

**Conclusion**

We conclude from the present study the greatest therapeutic efficacy of combined physical and medical treatment compared with each line alone in the management of pain and other inflammatory symptoms and in the prevention of complications in chronic PID patients.

Our study was met by some limitations as the small number of patients of the study groups and long time of their collection that caused by exclusion of PID patients with intrauterine device which is the most common cause of infection in women; also, the compliance of the patients to treatment was not very well and some patients were missed after receiving the half number of sessions; so, we exclude the patients who have not received proper treatment as mentioned in participants and methods of this article and this limited the number of our patients.

**Recommendation**

We recommend studying the therapeutic efficacy of other physical modalities such as magna-therapy and hydrotherapy and other forms of superficial heat therapy in the treatment of chronic PID as infrared regarding their physiological effects in the management of pain and inflammation and regarding their wide range of safety with less limitation of their applications compared with SWD.

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**Conflicts of interest**

There are no conflicts of interest.

**References**