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ORIGINAL CONTRIBUTION

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Power Doppler sonography in the evaluation and follow-up of knee involvement in patients with juvenile idiopathic arthritis

Power Doppler Sonographie in Auswertung und Katamnese des Befalls der Knie bei Patienten mit juveniler idiopathischer Arthritis

Summary *Introduction* This study was undertaken to evaluate the role of ultrasound (US), conventional color (CD) and power Doppler (PD) in the detection and quantification of inflammatory signs of the knee in children with juvenile idiopathic arthritis (JIA) and to correlate these findings with patient history, clinical, laboratory and radiological findings. *Patients and methods* Thirty patients with JIA who had clinical signs of knee involvement as well as 15 healthy children as a control group where subjected to full clinical examination and laboratory investigations on the same day of US examination. The knee joints were evaluated with plain radiography, US, and color Doppler in 13 patients, while the remaining 17 were assessed with power Doppler. Fourteen patients were subjected to follow-up assessment. *Results* A highly significant difference in synovial thickening and cartilage thickness detected by US between JIA affected knees and those of controls ($p < 0.0001$). Knee effusion was demonstrated in 93% of patients. Synovial vessles were detected by Doppler in 76.7% of patients. A significant correlation was detected between the degree of vascularity detected by PD and knee score ($p < 0.05$), and JAFAR score ($P < 0.05$). On comparing the findings of the follow-up with those of the initial examination, a significant positive correlation was detected between the differences in the knee score and those in synovial thickness ($p < 0.05$), and with the vascularity scale detected by PD ($p < 0.05$). *Conclusion* This study suggests the Doppler sonography as a non-invasive, low-cost, and readily available tool for the evaluation and follow-up of articular involvement in knees of JIA patients.

Key words Power doppler (PD) – color doppler (CD) – juvenile idiopathic arthritis (JIA) – ultrasound (US) – juvenile arthritis functional assessment report (JAFAR) – synovial vascularity

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Introduction

Juvenile idiopathic arthritis (JIA) is a idiopathic inflammatory disease primarily affecting joints with the synovium being the target tissue, but also extra articular tissue (1).

The knee is the joint most commonly affected and in many ways accounts for the most disability. The pathology of knee joint arthritis reflects a number of different but interrelated processes including inflammation (synovitis) leading to synovial proliferation, vascular changes (angiogenesis) and forma-

tion of highly cellular pannus that erodes the bone at the osteochondral junction, invades marrow space and undermines articular cartilage spreading across its edges towards the center (2).

Plain radiographs are non-specific until late stages of disease when bone erosions or joint space narrowing have occurred. Radiological damage thus represents the cumulative effects of the disease during the preceding period, but is independent of current disease activity (3).

US of the knee provides the ability to assess changes in the synovial membrane, the presence of joint effusion and changes in the articular cartilage; all of which can differentiate between active knee involvement and subjects in clinical remission (4).

Color Doppler US could be used to study the vascularization of the synovial membrane and periarticular tissue of the knee (5). Power Doppler sonography (PDS) is able to detect low levels of flow in tissue (tissue perfusion) independent of direction or vessel type (6). Power Doppler can also be used to visually quantify tissue flow in relation to disease activity (7).

In the present study patients with JIA have been involved. The correlation between different disease parameters and the soft tissue vascularity of the knee joint assessed by PDS have been studied.

Material and methods

Thirty patients with JIA (19 females, mean age 11.9 ± 3.7 years, range 1.3–16 years) fulfilled the criteria for the diagnosis of JRA (8) attending the Rheumatology and Rehabilitation outpatient clinic, Faculty of Medicine, Cairo University Hospital were selected for the present study. Patients with JIA who had never had clinical evidence of knee involvement were excluded.

Five patients had pauciarticular (oligoarticular) onset, 13 had polyarticular onset and 12 had systemic onset. All patients included in the study were having an active disease defined by the presence of synovitis on examination.

A group of 15 normal healthy children (mean age 9.1 ± 3.35, range 4-14) attending the hospital, as children of employees, served as controls. Permission was obtained from parents of all children.

Twenty one patients were receiving methotrexate (MTX), weekly i.m., and 16 were receiving oral steroids (Table 1). All patients had a complete clinical examination including evaluation for gastrointestinal, pulmonary, cardiac, renal, ocular and muscle involvement.

At the time of the radiological assessment the extent of articular involvement was assessed using the number of active joints defined as (soft tissue swelling or in the case of hips and shoulders, pain with loss of active movement). The Juvenile Arthritis Functional Assessment Report (JAFAR) was performed for all patients (9). Both knees were scored clinically according to Suerda et al., 1994 (10) by indicating the presence or absence of the following: Pain; 0 = absence, 1 = presence. The degree of swelling; 0 = absence, 1 = mild, 2 = moderate, 3 = severe. The degree of limitation of extension: 0 = no limitation, $1 < 5^\circ$ extension, $2 < 10^\circ$ extension, $3 < 15^\circ$ extension, $4 > 15^\circ$ extension. Patients with a mean score of ≥1 were classified as having active knee involvement, while patients with normal physical examination findings were considered to be in clinical remission. The more affected knee was involved in the study.

Routine laboratory examinations including complete blood picture, erythrocyte sedimentation rate (ESR), liver and kidney functions were performed. In addition to qualitative detection of C-reactive

Table 1 General features and drug intake of JIA patients

	All patients n = 30	Pauciarticular JIA N = 5	Polyarticular JIA N = 13	Systemic JIA N = 12
Sex male (%)	11(36.7)	3(60)	2(15.4)	6(50)
Age (year)	11.9 ± 3.7	9.9 ± 5.3	13.1 ± 2.5	11.4 ± 3.8
Age of onset (year)	8.1 ± 4.3	6.8 ± 4.4	10.4 ± 2.4	6.2 ± 4.8
Disease duration (year)	3.8 ± 3.2	3.1 ± 2.6	2.8 ± 2.1	5.2 ± 4.1
Morning stiffness (min)	75.5 ± 58.4	57 ± 58.5	73.5 ± 67.6	85.4 ± 49.9
Active joints (n)	4.5 ± 3.1	3.2 ± 2.3	4.8 ± 2.2	4.7 ± 4.1
JAFAR score (n)	10.5 ± 7.2	6.8 ± 7.6	10 ± 7.9	12.5 ± 6.1
Knee score (n)	4.1 ± 1.7	3.2 ± 1.9	3.8 ± 1.4	4.8 ± 1.7
MTX dose (mg/w)	6.7 ± 4.9	7 ± 4.6	5.8 ± 5.1	7.5 ± 5
MTX duration (year)	1.3 ± 1.5	1.6 ± 1.1	1.4 ± 2	1.2 ± 1.2
MTX cumulative dose (mg)	626.7 ± 841.6	648 ± 469	666.3 ± 1152.7	575 ± 576.9
Steroids daily dose (mg)	4.4 ± 6.4	1.5 ± 2.2	1.7 ± 3.7	8.5 ± 7.7
Steroids duration (year)	1 ± 1.5	0.7 ± 1	0.3 ± 0.5	1.9 ± 1.9
Intra-articular steroids (%)	8(26.7)	1(20)	2(15.4)	5(41.7)
Antimalarial (%)	16(53.3)	3(60)	7(53.9)	6(50)

protein (CRP) by the latex agglutination slide test, rheumatoid factor (RF) by the latex agglutination slide test (11) and circulatory anti-nuclear antibody (ANA) using the immunofluorescence (IF) technique (12) were determined.

Radiological assessment

Plain X-ray was done for the involved knee and was scored radiologically according to Petterson and Rydholm (13). Thirteen US scans were obtained with an ATL (Advanced Technology Laboratories, USA, Ultramark 9 HDI) equipped with a 5–10 MHz linear array transducer for musculoskeletal parts. The ATL is equipped with color Doppler and spectral analysis. The remaining 17 US scans were obtained with a SONOLINE Elegra, SIEMENS model (Siemens Medical System, Inc./Ultrasound Group) equipped with a 7–10 MHz linear array transducer for musculoskeletal parts. Elegra is also equipped with color, spectral, power Doppler and sea-scape (extended field). The length of time of examination was 15 min, on average.

A standardized procedure similar to that used Suerda et al., 1994 (10) was followed. Initially, sets of sagittal images of the suprapatellar bursa were obtained with the patient in the recumbent position, with the knee at 30° of flexion. The US transducer was positioned longitudinally above the patella, and the synovial membrane was measured when the probe touched the middle portion of the basis patellae. Measurement of total synovial thickness (with electronic calipers), which corresponded to the largest anteroposterior diameter of the suprapatellar pouch, was performed by applying firm compression with the transducer to express the suprapatellar fluid into the joint recesses.

Assessment of intraarticular fluid was performed by measuring the length of the suprapatellar bursa. Longitudinal images were obtained with manual compression of the lateral synovial recesses to express all intraarticular fluid into the suprapatellar bursa. Transverse diameters were also obtained in the longitudinal images followed by depth measurements in the transverse images. Furthermore the volume of fluid was calculated by using the elliptical formula. The presence of any loculations or internal echoes was documented.

Femoral condylar cartilage was assessed with the knees flexed as much as the patient's illness would permit. The transducer was positioned transversely above the patella in the middle line in the intercondylar notch. The thickness of the cartilage at the level of the medial and lateral femoral condyles was measured with electronic calipers. The sharpness of the margins of the cartilage and presence of erosions were also evaluated. Finally, the presence or absence of Baker cysts and popliteal lymph nodes were assessed with the patient in the prone position.

Color Doppler imaging was performed on thirteen patients (standardized with a pulse repetition frequency of 900–1500 Hz). Power Doppler imaging was performed on the remaining 17 patients (standardized with a pulse repetition frequency of 900–1000 Hz). The Doppler studies were done for the supra-patellar pouch by selecting a region of interest that included soft tissue and underlying bone immediately above the patella. Color gain was initially set at a level just below the disappearance of color noise deep to the cortical bone; this setting resulted in gains of 110–112 dB. Representative power Doppler images were documented by printing hard copies on a color laser printer (CP700 Mitsubishi color printer). The degree of vascularity was graded on a scale of 1–4 used by Newman et al. (14).

This was followed by manually directing the sample volume to the synovial vessels and spectral analysis was done. The peak systolic and end-diastolic measurements were determined by electronic caliper. The resistivity index (RI) was determined for each wave and the number of vessels were calculated.

Follow-up

Our follow-up group consisted of 14 of the JIA patients. Five of these patients received intra-muscular injection of steroids (Sterile Triamcinolone Acetonide Suspension, 40 mg) as a bridging therapy, 3 patients underwent aspiration of their knee effusion and were injected with steroids (Sterile Triamcinolone Acetonide Suspension, 40 mg) intra-articularly under aseptic conditions, and the remaining 6 patients received no alteration in therapy. All patients were reexamined after one week.

The follow-up consisted of re-evaluation by the same rheumatologists (A.S., S.E.) of the clinical activity of the disease, in particular the knee score, then complete US examinations were performed on all 14 knees followed by Doppler evaluation using the type of Doppler used in the initial examination (7 with PD). One radiologist (A.H.) performed all sonographic examinations. Images were reviewed by two radiologists (E. E., A. H.).

Statistical analysis

Data were reported as mean ± standard deviation. The analysis of variance (ANOVA) and chi-squared test with Yates' correction and Fisher's exact test were used when appropriate. The correlation coeffi-

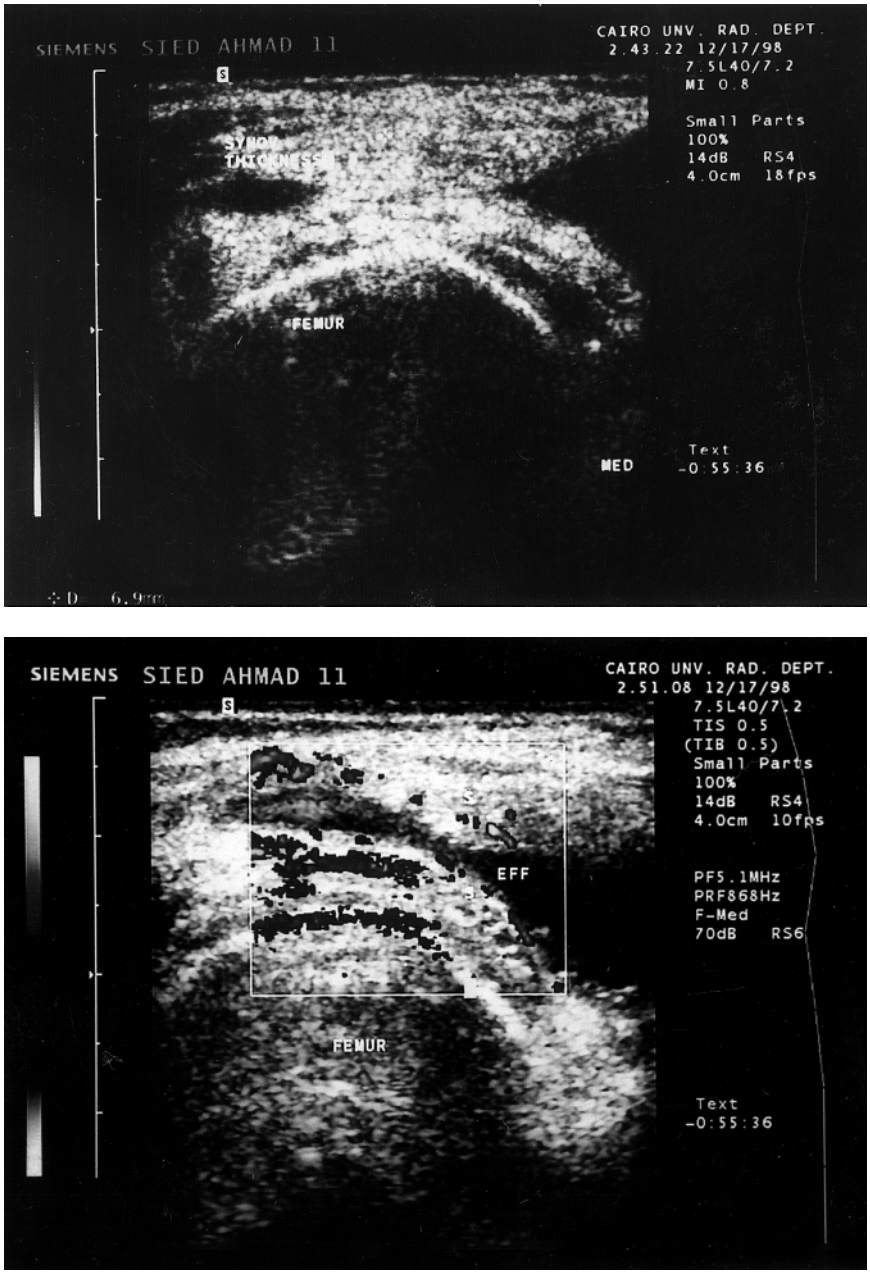

Fig. 1 a Longitudinal gray-scale US at the suprapatellar region showing one of the most unique features of US; its real time capability and manual expression of the hand-held probe allowed coaptation of the synovial surfaces facilitating accurate synovial thickness measurement. **b** Transverse power Doppler image at the region of the suprapatellar bursa of the same patient showing moderate to marked synovial hyperemia (vascularity; *EFF* effusion)

cient (r) was calculated utilizing Pearson's correlation. The correlation between continuous variables was evaluated by linear regression analysis.

Results

General characteristics are shown in Table 1. Laboratory and radiological findings are shown in Table 2.

Ultrasound findings

The synovium was arranged in linear sheets in all patients. In addition 12 (40%) patients had synovial nodules, 9 (30%) had synovial proliferation in the form of fibrous strands and 5 (16.7%) had synovial villi. Ultrasound findings in patients and controls are shown in Table 3.

In this study, none of knees in the control subjects showed knee effusion, whereas it was demonstrated in most of our patients (93%) with two ex-

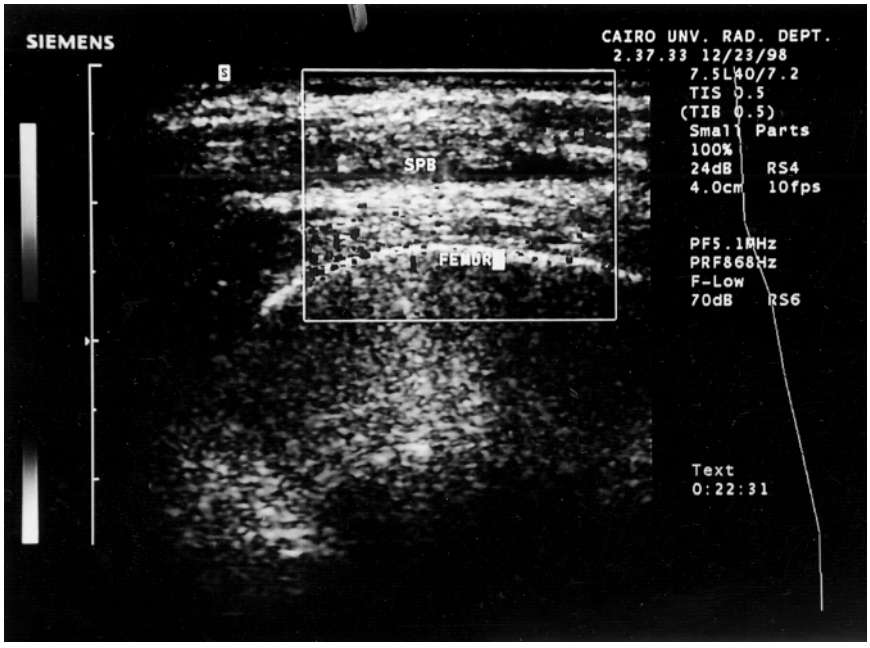

Fig. 1 c PDS of the same patient one week post-intramuscular steroid injection; apparent reduction of synovial vascularity is evident. Reduced amount of joint effusion is also noted. (*SPB* suprapatellar bursa)

Table 2 Laboratory and radiological findings of JIA patients

	All patients n = 30	Pauciarticular JIA N = 5	Polyarticular JIA N = 13	Systemic JIA N = 12
Hemoglobin	10.1 ± 1.5	10.4 ± 1.4	10.1 ± 1.5	10 ± 1.7
WBCs	7.8 ± 2.7	10 ± 3.6	7.1 ± 2.3	7.7 ± 2.4
Platelets count	400.2 ± 146.8	319.8 ± 147.3	405.4 ± 106.6	428 ± 180.9
ESR	64.8 ± 38.6	53.2 ± 47.2	68 ± 34.6	66.2 ± 41.7
CRP positive n (%)	23(76.7)	4(80)	10(76.9)	9(75)
RF positive n (%)	10(33.3)	1(20)	8(61.5)	1(8.3)
ANA positive n (%)	5(16.7)	1(20)	2(15.4)	2(16.7)
Plain radiography score	7 ± 1.7	6.4 ± 1.8	6.8 ± 1.4	7.4 ± 1.9

ceptional cases considered clinically as having effusion, but no fluid was detected by US. These two cases had marked synovial thickening. Three other patients were not detected clinically as having effusion and were discovered by US. The volume of the fluid in the supra-patellar bursa ranged between 0.5–11 ml with a mean of 3.7 ± 0.5 ml in JIA affected knees. An anechoic fluid-filled bursa was apparent in patients with joint effusion. The margins of the supra-patellar bursa were irregular due to a certain degree of synovial proliferation in association with joint effusion. In healthy children, visualization of the fluid in supra-patellar bursa may be difficult due to the minute amount of fluid normally present. The length of the supra-patellar bursa was measured in 9 of the healthy children, with a mean of 1.7 ± 0.4 cm (range 1.3–2.3). In 16 patients (53%), the effusion was not homogenously echoelucent exhibiting fine, multiple echoes (loose bodies) known to occur in different forms of arthritis (internal echoes) (IE). In this study Baker cysts were visualized as anechoic fluid collections, in the popliteal fossa, with marked irregularities in the margins caused by synovial proliferation. Baker cysts were documented in 3 (10%) JIA patients with a mean fluid content of 2.5 ml. These Baker cysts were not detected clinically. Baker cysts were not documented in any patient of the control group. Joint effusions were present in all patients with Baker cysts. A communicating gastrocnemius-semimembranous bursa was detected in 2 of the 3 Baker cysts.

A significant correlation was found between the effusion volume and number of swollen joints ($r = +0.39$, $p < 0.05$), and negatively with MTX intake duration ($r = -0.36$, $p < 0.05$). Loculations of effusion were correlated significantly with Knee score ($r = +0.36$, $p < 0.05$), JAFAR score ($r = +0.47$, $p < 0.01$), and negatively with ANA ($r = -0.41$, $p < 0.05$). Baker cyst detection correlated significantly with morning stiffness duration ($r = +0.49$, $p < 0.01$)

Table 3 Ultrasound findings in JIA patients

	All patients n = 30	Pauciarticular JIA N = 5	Polyarticular JIA N = 13	Systemic JIA N = 12	P
Synovial thickness (cm)*	0.8 ± 0.5	1 ± 0.6	0.6 ± 0.2	0.9 ± 0.6	0.0001
Effusion volume (ml)*	3.7 ± 2.7	2.1 ± 1.6	3.4 ± 2.8	4.6 ± 2.7	0.007
Loculation of effusion n** (%)	10(33.3)	0	3(23.1)	7(58.3)	0.05
IE n** (%)	16(53.3)	3(60)	7(53.9)	6(50)	NS
Baker cyst n** (%)	3(10)	1(20)	2(15.4)	0	NS
Lymph node n** (%)	1(3.3)	0	1(7.7)	0	NS
C of medial condyle thickness(mm)*	2.9 ± 0.9	3.3 ± 0.8	2.9 ± 0.7	2.8 ± 1.2	0.003
C of lateral condyle thickness (mm)*	2.8 ± 1.1	2.9 ± 1.3	2.8 ± 0.8	2.7 ± 1.3	0.02
Cartilage IE n** (%)	14(46.7)	1(20)	6(64.2)	7(58.3)	NS

C cartilage, *IE* internal echoes. ANOVA* and chi-squared test** were used

and ESR ($r = +0.36$, $p < 0.05$). Cartilage thickness showed a significant negative correlation with disease duration ($r = -0.45$, $p < 0.05$).

Color Doppler

Synovial vessles were detected in 10 (76.9%) of the 13, a hypervascular pattern resulting from hyperemia associated with inflammation and synovial neoangiogenesis. In these patients, the number of synovial vessels ranged between 2–5 synovial vessels with a mean of 3.1 ± 0.88 synovial vessels. Spectral analysis detected both venous and arterial, but mainly arterial waveforms with lower resistance than normal (RI ranging from 0.53–0.77) with a mean of 0.66 ± 0.1.

In this study, the number of synovial vessels detected by color Doppler revealed a positive significant correlation with the loculation of effusion in the supra-patellar bursa ($P < 0.05$).

Power Doppler

Synovial vessles were detected in 13 (76.5%) knees of the 17 patients, ranging from 1–5 vessles in the selected region in each patient, with a mean of 2.5 ± 1.1 synovial vessles, while RI ranged between 0.53–0.78 with a mean value of 0.66 ± 0.07. The degree of vascularity of the synovium lining the supra-patellar bursa was assessed, with a mean scale of 2.6 ± 1 (range 1–4).

A positive significant correlation was found between the degree of vascularity (PD) and each of the following: knee score ($r = +0.56$, $p < 0.05$), and JAFAR score ($r = +0.52$, $p < 0.05$) and the effusion volume ($r = +0.61$, $p < 0.01$) as well as the effusion loculation detected by US ($r = +0.81$, $p < 0.01$). A negative significant correlation was found with ANA ($r = -0.65$, $p < 0.01$).

Loculation of effusion shown by US, number of synovial vessels, degree of vascularity and resistivity index (RI) detected by power Doppler, as well as plain radiography score showed a significantly negative correlation with seropositivity of ANA in JIA patients ($P < 0.05$, $P < 0.05$, $P < 0.01$, $P < 0.01$, $P < 0.01$ respectively).

Follow-ups

On follow-up examinations of 14 JIA patients, clinical improvement was noticed in 13 of the JIA patients. The clinical improvement was associated with decrease of synovial thickness in 13 (92.9%) JIA knees, and decrease of effusion volume was observed in 13 (92.9%) knees. The decrease in number of synovial vessels was detected in 11 (78.6%) knees, with complete absence of detectable synovial vessels in 4 (28.6%) patients. The RI of these synovial vessels increased in 6 of the JIA patients, decreased in 3 JIA patients and was unaltered in one JIA patient. In the 7 follow-up examinations done by power Doppler, the degree of vascularity of the synovium decreased in 7 (100%) JIA affected knees.

When comparing the findings of the follow-up and the initial examination, the difference in the knee score of all follow-ups correlated significantly positive with the difference in synovial thickness ($r = +0.81$, $p < 0.05$) and the difference in synovial vascularity scale detected by PD ($r = +0.84$, $p < 0.05$).

A positive significant correlation was also found between the difference in knee score and the difference in interventional therapy ($P < 0.05$). Knee score improvements were mostly seen in patients who received knee intra-articular steroid injections and aspiration of joint fluids, followed by those who received intra-muscular steroid injections, followed by those who received no alteration in management.

Discussion

Although previous studies have shown that the extent of changes in JIA are better seen with MRI (15, 16). MRI is also expensive and time-consuming, and subsequently not suitable as a monitoring follow-up method (17).

In agreement with the previous US studies of the knee, this study provided the ability to assess the proliferation and the shape of the synovium, the presence of joint effusion, the presence of supra-patellar effusion (4, 10) and changes in the articular cartilage (4, 10, 18); all of which can differentiate between active knee involvement and subjects in clinical remission. Although it may be possible to distinguish effusion from thickening of the synovial membrane by patellar ballottement, differentiation may be easily and reliably obtained by US. Furthermore, even if differentiation between active and quiescent disease is often possible based on clinical features, the quantitative assessment of both synovial effusion and thickening may play a useful role in supporting the clinical data, especially in mild forms (18).

Color Doppler in agreement with previous studies (5) was effective in studying the vascularization of the synovial membrane and the periarticular tissues of the knees.

A preliminary investigation performed by Newman et al. (14) suggested a role for power Doppler sonography in assessment of serial changes in synovial inflammation. However, one of the main limitations was the fact that assessment of hypervascularity was qualitative, which might result in substantial interobserver variability and prevent distinction between cases with subtle differences in perfusion. In a trial to overcome that limitation in the present study, actual sampling of the apparent hypervascularity sites and analysis of the waveform of these vessels were performed using spectral analysis and their RI was measured.

The degree of vascularity and RI detected by power Doppler revealed a negative significant correlation with the age of JIA patient ($P < 0.01$), ($P < 0.05$). It is not yet clear whether this finding is exclusive to patients with JIA or represents a generalized phenomenon with age.

A positive significant correlation was found between the degree of vascularity detected by power Doppler and the knee score ($P < 0.05$), JAFAR score ($P < 0.05$), and the effusion volume ($P < 0.01$) as well as the effusion loculation detected by US ($P < 0.01$). These findings in agreement with Newman et al. (14), suggest that the degree of vascularity detected by power Doppler may allow assessment of disease activity and therapeutic efficacy, as well as progression of disease.

Loculation of effusion shown by US, number of synovial vessels, degree of vascularity and resistivity index (RI) detected by power Doppler, as well as plain radiography score showed a significantly negative correlation with seropositivity of ANA in JIA patients ($P < 0.05$, $P < 0.05$, $P < 0.01$, $P < 0.01$, $P < 0.01$ respectively). The lower affinity of anti-single-stranded DNA and ANA, in comparison with the anti-DNA antibodies of those from systemic lupus erythematosus (SLE) patients, may be a consequence of polyclonal B cell activation, which is one of the immune abnormalities found in early rheumatoid arthritis JRA (19).

When comparing the findings of the first follow-up and the initial examination, the difference in the knee score correlated significantly positive with the difference in synovial thickness ($P < 0.05$), and also with the difference in vascularity scale detected by power Doppler ($P < 0.05$).

These findings stress the role suggested by previous studies (14) of power Doppler, and to a lesser extent US (4, 10, 18), in the follow-up of JIA patients, and in the monitoring of disease activity and therapy.

Given the difficulties of deciding whether a patient is in remission, detection of persistent synovial vascularity, or to a lesser extent, the detection of persistent fluid in the supra-patellar bursa or/and an increase in the synovial thickness may be considered indicative of continuing activity of the disease process. These findings may be particularly useful in patients with JIA who have no clinical evidence of knee involvement, equivocal symptoms, and negative laboratory findings for active disease and in whom treatment options are usually advocated empirically. In this context, Doppler sonography provides a more rational basis for the decision to maintain medications or to modify the current treatment approach.

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