Ultrasound imaging for the rheumatologist XIV. Ultrasound imaging in connective tissue diseases

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ABSTRACT

Ultrasound (US) role is becoming more and more relevant in the assessment of rheumatic diseases but there are still some almost unexplored fields and, surely, one of these is represented by the great family of connective tissue diseases (CTD). In this review we provide an update of the available data regarding some applications of US in CTD. Besides an overview of the role of US in their musculoskeletal involvement, we will report data on the use of US in the evaluation of skin and lung in systemic sclerosis and of salivary glands in Sjögren's syndrome. US assessment of heart, kidney or vascular involvement in CTD will not be the subjects of this paper.

Introduction

Several papers describe the clinical applications and findings of musculoskeletal ultrasound (US) (1-8) in patients with arthritides, predominantly rheumatoid arthritis (9) but also spondyloarthritis (10), osteoarthritis (11) and crystal-related arthritis (12). US has also been successfully applied to image multisystem involvement (heart, kidney and vessels) typical of connective tissue disorders (CTD) such as systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), systemic sclerosis (SSc), polymyositis (PM), dermatomyositis (DM), mixed connective tissue disease (MCTD) and undifferentiated connective tissue disease (UCTD). To date, very few studies are reported in the literature about the applications of US in the assessment of joint and tendon involvement in the course of CTD.

In this review we provide an update of the available data regarding some applications of US in CTD. Besides an overview of the role of US in musculoskeletal involvement in CTD we will report data on the use of US in the evaluation of skin and lung in SSc and of salivary glands in SS. US assessment of heart, kidney or vascular involvement in CTD will not be the subjects of this paper.

Systemic lupus erythematosus

Joint involvement in SLE patients is very frequent, particularly at the wrists and hands. It may range from mild arthralgia to severe non erosive deforming arthritis (Jaccoud's arthropathy), erosive arthritis resembling rheumatoid arthritis or mild deforming arthropathy (13). To the best of our knowledge, only two papers on SLE joint involvement evaluated by musculoskeletal US are reported in literature. In 2004, Iagnocco *et al*. examined 52 wrists of 26 SLE patients and demonstrated synovitis in 22/52 radio-ulno-carpal joints with synovial proliferation in 10 joints, effusion in 13, power Doppler signal in 5 and bone erosions in both wrists of the same patient (14). More recently, an ultrasound pictorial assay on hand and wrist arthritis in SLE showed joint effusion or synovial proliferation in 16 of 17 patients at the wrist and at the metacarpo-phalangeal joints (MCP) in 12, bone erosions of the 2nd and 3rd MCP joints in 8 subjects and finger flexor tenosynovitis in 11 patients (15). An interesting application of US coupled with color and power Doppler has been reported in 22 patients affected by SLE which showed hemodynamic changes in blood flow to the proximal femur even in the absence of osteonecrosis. The Authors suggest color Doppler evaluation of femoral head perfusion as a predictive test for hemodynamic deterioration (16).

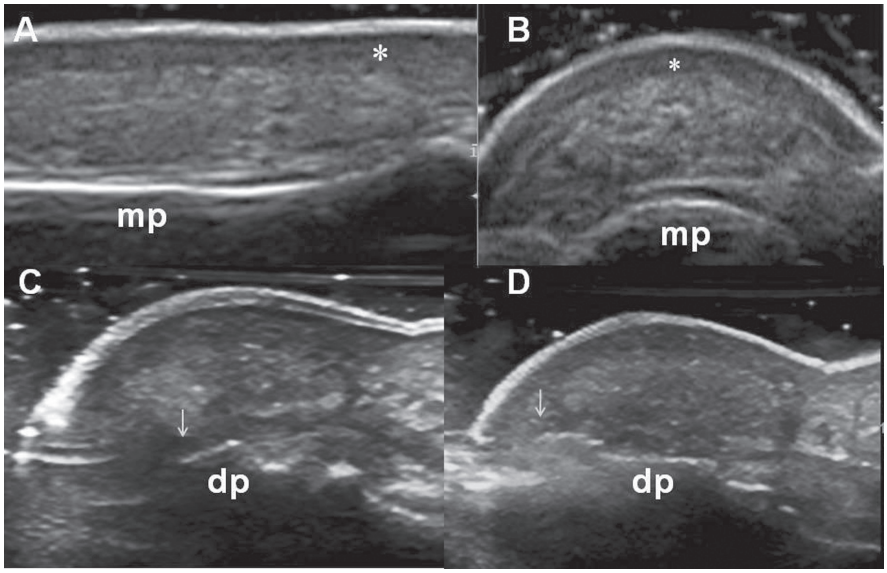

Fig 1. Systemic sclerosis. Dorsal longitudinal (**A**) and transverse (**B**) views of the 3rd finger. The asterisk indicates hypoechoic thickening of the derma due to edema. **mp** = middle phalanx. Images taken using a MyLab70 XVG (Esaote Biomedica, Genoa – Italy) equipped with a 6-18 MHz linear probe. Volar longitudinal views of the right (**C**) and left (**D**) 2nd finger with right distal phalanx bone resorption. The arrow indicates distal phalanx edge. **dp** = distal phalanx. Images taken using a Logiq 9 (General Electrics, Milwakee – USA) equipped with a 15 MHz linear probe.
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Table I. The US features which can be assessed in the salivary glands.

- Parenchymal echogenicity
- Homogeneity
- Presence of hypoechogenic areas
- Hyperechogenic lines and/or dots
- Clarity of glandular boundaries

Systemic sclerosis

Several features of SSc can be assessed using US including joint and tendon involvement, the presence of subcutaneous calcification and the skin features. To date only one study has investigated the role of US in the evaluation of SSc joints showing, at the distal phalanx of the hand, that the most frequent findings are soft tissue calcifications and narrowing of the distance between phalangeal apex and skin surface (17). No US studies have been published on tendon involvement in SSc. Subcutaneous calcification, even when incipient, can be imaged, using US, particularly over the palmar aspect of the finger (18). Dermatological US was initiated in 1979 by Alexander and Miller who measured skin thickness by a 15 MHz US (19). The development of very high frequency probes (20 MHz or more), which are mandatory to clearly distinguish epidermidis, dermis and subcutaneous fat, has allowed not only the determination of thickness but also a qualitative assessment of the skin. Thus, in recent times, several papers have reported the sonographic skin findings in diffuse or localized scleroderma (20-24). However, lack of homogeneity among the different studies exists: firstly, the frequency of the probes used ranged from 10 to 32 MHz and, in addition, inconsistencies relating to the skin depth examined. In 2003, a longitudinal study (using a 20 MHz ultrasound probe) in 16 patients (8 with diffuse and 8 with limited SSc) showed thickening and decreased echogenicity of the dermis in sclerotic skin in the early phases of the diseases. The degree of thickening tended to diminish with time and, at 4 years of disease duration, thickness was significantly decreased in the forearm and chest and echogenicity increased at the hands. The Authors concluded that US appeared as a good non-invasive tool to monitor disease progression (25).

A 17-point dermal US scoring method has been proposed (using a 22 MHz US probe) based on the measurement of dermal thickness at 17 sites, corresponding to those of the modified Rodnan skin score. This scoring system may be a useful measure of outcome in the future (26).

In SSc patients with short disease duration, US has been shown to be able to detect the oedematous phase that may precede palpable skin involvement, that could be useful in identifying patients with diffuse skin involvement in a very early disease phase (27).

Recently quantitative US has shown a decrease in the skin thickness after photochemotherapy in SSc (28). The application of US in the evaluation of lung fibrosis in SSc patients is under investigation. It would appear that both pleural effusion and interstitial change can be identified using US and has been proposed as a possible alternative to high resolution computed tomography in the follow-up of such patients (29, 30).

Sjögren's syndrome

Joint involvement is not rare in SS (31) and US can be useful in its evaluation and also to investigate changes in salivary gland architecture. Iagnocco *et al.* studied knee involvement in patients with primary and secondary SS (associated with rheumatoid arthritis or CTD). They demonstrated mild synovitis in primary SS while joint effusion was more frequently present in secondary SS with rheumatoid arthritis (32). Several studies based on the US findings in the parotid and submandibular glands in primary SS have been published (33-37). US examination of the salivary glands is performed using a 5-14 MHz linear transducer to assess the following parameters*:* parenchymal echogenicity, homogeneity, the presence of hypoechogenic areas, hyperechogenic lines and/or dots, clarity of the glandular boundaries (see Table I). A reproducible scoring system (range 0 to 3) has been proposed by Hocevar *et al*. (38, 39) and by Wernicke *et al*. (range 0 to 2) (40). A further scoring system comparing US findings with minor salivary gland biopsy, proposed a US score (range 0 to 4) which assigned points to the different degrees of glandular inhomogeneity (41). Recently, Shimizu *et al*. tried to precisely define what "inhomogeneity"

means and suggested a further grading (positive, probable and negative) (42). In comparison to other imaging tools, such as sialography, scintigraphy and MRI, US emerges as a very useful method for the diagnosis and follow-up of salivary gland involvement in SS patients (43-45). Color Doppler sonography has investigated blood flow before and after secretory stimulation and shows that blood flow response may be defective in the salivary glands of these patients (46).

Changes within the lacrimal glands in SS have been studied and demonstrated significant differences in size compared to normal subjects together with changes in echostructure due to fatty infiltration or the presence of lymphoma. US was not able to accurately image atrophic glands due to their size and their isoechoic pattern indiscernible from orbital fatty tissue (47).

Polymyositis and dermatomyositis

Very few studies are reported on the role of musculoskeletal US in PM and DM. However, using a 7-9 MHz linear transducer array it is possible to evaluate muscle changes in myositis. With normal muscle bulk, fascicles appear anechoic or hypoechoic relative to septae. An isoechoic appearance is considered extremely abnormal, reflecting diminished fascical size and closer space between fibrous septae. Reimers *et al*. (48) reported muscle atrophy and increased echogenicity in the upper and lower limbs both in childhood and adult PM and DM. Higher echogenicity and more pronounced atrophy was usually present in chronic myositis, lower echogenicity and muscle edema in acute myositis (48). In another study in 37 patients with DM or PM, the gray-scale evaluation of muscle was correlated with power Doppler. Disease of longer duration was significantly associated with more abnormal features on gray-scale examination, whilst power Doppler signal was increased in disease of shorter duration (49). Recently using contrast-enhanced US, muscle perfusion was studied in 35 patients suspected of having PM and DM. In all patients, blood flow, volume and flow velocity were measured and compared to the results of MRI and muscle biopsy. Eleven out of 35 patients had histologically confirmed DM or PM and significantly higher perfusion parameters. The Authors concluded that contrast-enhanced US could be an additional parameter for the diagnosis of inflammatory myopathy (50). US can also be useful to aid needle positioning during muscle biopsy, however, MRI is still considered more sensitive than US in the detection of muscle edema. Calcification can easily be detected because of high echointensity and acoustic shadowing on US images (48).

Undifferentiated and mixed connective tissue disease

Very recently, a study on 14 UCTD patients suggested that power Doppler US has better accuracy than nailfold capillaroscopy in differentiating primary from secondary Raynaud's phenomenon and in assessing microvascular abnormalities (51).

Research agenda

Future areas for researchers to target in this field include:

- Definition of the features of the articular and periarticular involvement in all CTD.
- Standardization of the scanning protocol of the skin.
- Study of the features of skin involvement in SSc and MCTD.
- Evaluation of diagnostic accuracy and follow-up of skin US.
- Study of muscle involvement not only in PM and DM but also in myositis associated with SLE and SSc using US and power Doppler examination.
- Development of largely accepted criteria to diagnose SS even in the absence of minor salivary glands biopsy.
- Role of US in the therapy monitoring of the different manifestations of CTD.

Link

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References

1. FILIPPUCCI E, IAGNOCCO A, MEENAGH G *et al*.: Ultrasound imaging for the rheumatologist. *Clin Exp Rheumatol* 2006; 24: 1-5.
2. IAGNOCCO A, FILIPPUCCI E, MEENAGH G *et al*.: Ultrasound imaging for the rheumatologist. I. Ultrasonography of the shoulder. *Clin Exp Rheumatol* 2006; 24: 6-11.
3. FILIPPUCCI E, IAGNOCCO A, MEENAGH G *et al*.: Ultrasound imaging for the rheumatologist II. Ultrasonography of the hand and wrist. *Clin Exp Rheumatol* 2006; 24: 118-22.
4. IAGNOCCO A, FILIPPUCCI E, MEENAGH G *et al*.: Ultrasound imaging for the rheumatologist III. Ultrasonography of the hip. *Clin Exp Rheumatol* 2006; 24: 229-32.
5. MEENAGH G, IAGNOCCO A, FILIPPUCCI E *et al*.: Ultrasound imaging for the rheumatologist IV. Ultrasonography of the knee. *Clin Exp Rheumatol* 2006; 24: 357-60.
6. RIENTE L, DELLE SEDIE A, IAGNOCCO A *et al*.: Ultrasound imaging for the rheumatologist V. Ultrasonography of the ankle and foot. *Clin Exp Rheumatol* 2006; 24: 493-8.
7. DELLE SEDIE A, RIENTE L, IAGNOCCO A *et al*.: Ultrasound imaging for the rheumatologist. VI. Ultrasonography of the elbow, sacroiliac, parasternal, and temporomandibular joints. *Clin Exp Rheumatol* 2006; 24: 617-21.
8. IAGNOCCO A, FILIPPUCCI E, MEENAGH G *et al*.: Ultrasound imaging for the rheumatologist. XI. Ultrasound imaging in regional pain syndromes. *Clin Exp Rheumatol* 2007; 25: 672-5.
9. FILIPPUCCI E, IAGNOCCO A, MEENAGH G *et al*.: Ultrasound imaging for the rheumatologist VII. Ultrasound imaging in rheumatoid arthritis. *Clin Exp Rheumatol* 2007; 25: 5-10.
10. RIENTE L, DELLE SEDIE A, FILIPPUCCI E *et al*.: Ultrasound imaging for the rheumatologist IX. Ultrasound imaging in spondyloarthritis. *Clin Exp Rheumatol* 2007; 25: 349-53.
11. MEENAGH G, FILIPPUCCI E, IAGNOCCO A *et al*.: Ultrasound imaging for the rheumatologist VIII. Ultrasound imaging in osteoarthritis. *Clin Exp Rheumatol* 2007; 25: 172-5.
12. DELLE SEDIE A, RIENTE L, IAGNOCCO A *et al*.: Ultrasound imaging for the rheumatologist X. Ultrasound imaging in crystal-related arthropathies. *Clin Exp Rheumatol* 2007; 25: 513-7.
13. MARTINEZ JB, VALERO JS, BAUTISTA AJ *et al*.: Erosive arthropathy: clinical variance in lupus erythematosus and association with anti-CCP case series and review of the literature. *Clin Exp Rheumatol* 2007; 25: 47-53.
14. IAGNOCCO A, OSSANDON A, COARI G *et al*.: Wrist joint involvement in systemic lupus erythematosus. An ultrasonographic study. *Clin Exp Rheumatol* 2004; 22: 621-4.
15. WRIGHT S, FILIPPUCCI E, GRASSI W, GREY A, BELL A: Hand arthritis in systemic lupus erythematosus: an ultrasound pictorial essay. *Lupus* 2006; 15: 501-6.
16. LEE CW, KIM HJ, SHIN MJ: Evaluation of haemodynamic flow to the hip in patients with systemic lupus erythematosus. *Scand J Rheumatol* 2007; 36: 36-9.
17. GRASSI W, FILIPPUCCI E, FARINA A, CERVINI C: Sonographic imaging of the distal phalanx. *Semin Arthritis Rheum* 2000; 29: 379-84.
18. BOUTRY N, HACHULLA E, ZANETTI-MUSIELAK C, MOREL M, DEMONDION X, COTTEN A: Imaging features of musculoskeletal involvement in systemic sclerosis. *Eur Radiol* 2007; 17: 1172-80.
19. ALEXANDER H, MILLER DL: Determining

skin thickness with pulsed ultrasound. *J Invest Dermatol* 1979; 72: 17-9.
20. MYERS SL, COHEN JS, SHEETS PW, BIES JR: B-mode ultrasound evaluation of skin thickness in progressive systemic sclerosis. *J Rheumatol* 1986; 13: 577-80.
21. IHN H, SHIMOZUMA M, FUJIMOTO M *et al*.: Ultrasound measurement of skin thickness in systemic sclerosis. *Br J Rheumatol* 1995; 34: 535-8.
22. SCHEJA A, AKESSON A: Comparison of high frequency (20 MHz) ultrasound and palpation for the assessment of skin involvement in systemic sclerosis (scleroderma). *Clin Exp Rheumatol* 1997; 15: 283-8.
23. SZYMANSKA E, NOWICKI A, MLOSEK K *et al*.: Skin imaging with high frequency ultrasound - preliminary results. *Eur J Ultrasound* 2000; 12: 9-16.
24. KANE D, BALINT PV, STURROCK R, GRASSI W: Musculoskeletal ultrasound – a state of the art review in rheumatology. Part 2: Clinical indications for musculoskeletal ultrasound in rheumatology. *Rheumatology* 2004; 43: 829-38.
25. AKESSON A, HESSELSTRAND R, SCHEJA A, WILDT M: Longitudinal development of skin involvement and reliability of high frequency ultrasound in systemic sclerosis. *Ann Rheum Dis* 2004; 63: 791-6.
26. MOORE TL, LUNT M, MCMANUS B, ANDERSON ME, HERRICK AL: Seventeen-point dermal ultrasound scoring system - a reliable measure of skin thickness in patients with systemic sclerosis. *Rheumatology* (Oxford) 2003; 42: 1559-63.
27. HESSELSTRAND R, SCHEJA A, WILDT M, ÅKESSON A: High-frequency ultrasound of skin involvement in systemic sclerosis reflects oedema, extension and severity in early disease. *Rheumatology* 2008; 47: 84-7.
28. HASHIKABE M, OHTSUKA T, YAMAZAKI S: Quantitative echographic analysis of photochemotherapy on systemic sclerosis skin. *Arch Dermatol Res* 2005; 296: 522-7.
29. LICHTENSTEIN DA: Ultrasound in the management of thoracic disease. *Crit Care Med* 2007; 35 (Suppl. 5): S250-61.
30. DOVERI M, FRASSI F, CONSENSI A *et al*.: Le comete ultrasoniche polmonari: un nuovo segno ecografico di fibrosi polmonare nella sclerodermia. *Reumatismo* 2007; 59 (numero speciale 2): 12.
31. HAGA HJ, PEEN E: A study of the arthritis pattern in primary Sjögren's syndrome. *Clin Exp Rheumatol* 2007; 25: 88-91.
32. IAGNOCCO A, COARI G, PALOMBI G, VALESINI G: Knee joint synovitis in Sjögren's syndrome. Sonographic study. *Scand J Rheumatol* 2002; 31: 291-5
33. DE VITA S, LORENZON G, ROSSI G, SABELLA M, FOSSALUZZA V: Salivary gland echography in primary and secondary Sjögren's syndrome. *Clin Exp Rheumatol* 1992; 10: 351-6.
34. CAROTTI M, SALAFFI F, MANGANELLI P, ARGALIA G: Ultrasonography and colour doppler sonography of salivary glands in primary Sjögren's syndrome. *Clin Rheumatol* 2001; 20: 213-9.
35. MADANI G, BEALE T: Inflammatory conditions of the salivary glands. *Semin Ultrasound CT MR* 2006; 27: 440-51.
36. ALYAS F, LEWIS K, WILLIAMS M *et al*.: Diseases of the submandibular gland as demonstrated using high resolution ultrasound. *Br J Radiol* 2005; 78: 362-9.
37. CHIKUI T, OKAMURA K, TOKUMORI K *et al*.: Quantitative analyses of sonographic images of the parotid gland in patients with Sjogren's syndrome. *Ultrasound Med Biol* 2006; 32: 617-22.
38. HOCEVAR A, AMBROZIC A, ROZMAN B, KVEDER T, TOMSIC M: Ultrasonographic changes of major salivary glands in primary Sjogren's syndrome. Diagnostic value of a novel scoring system. *Rheumatology* (Oxford) 2005; 44: 768-72.
39. HOCEVAR A, RAINER S, ROZMAN B, ZOR P, TOMSIC M: Ultrasonographic changes of major salivary glands in primary Sjögren's syndrome. Evaluation of a novel scoring system. *Eur J Radiol* 2007; 63: 379-83.
40. WERNICKE D, HESS H, GROMNICA-IHLE E, KRAUSE A, SCHMIDT A: Ultrasonography of salivary glands – a highly specific imaging procedure for diagnosis of Sjögren syndrome. *J Rheumatol* 2008; 35: 285-93.
41. SALAFFI F, ARGALIA G, CAROTTI M, GIANNINI FB, PALOMBI C: Salivary gland ultrasonography in the evaluation of primary Sjögren's syndrome. Comparison with minor salivary gland biopsy. *J Rheumatol* 2000; 27: 1229-36.
42. SHIMIZU M, OKAMURA K, YOSHIURA K, OHYAMA Y, NAKAMURA S, KINUKAWA N: Sonographic diagnostic criteria for screening Sjögren's sindrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; 102: 85-93.
43. MAKULA E, POKORNY G, KISS M *et al*.: The place of magnetic resonance and ultrasonographic examinations of the parotid gland in the diagnosis and follow-up of primary Sjögren's syndrome. *Rheumatology* (Oxford) 2000; 39: 97-104.
44. NIEMELÄ RK, TAKALO R, PÄÄKKÖ E *et al*.: Ultrasonography of salivary glands in primary Sjogren's syndrome. A comparison with magnetic resonance imaging and magnetic resonance sialography of parotid glands. *Rheumatology* (Oxford) 2004; 43: 875-9.
45. EL MIEDANY YM, AHMED I, MOURAD HG *et al*.: Quantitative ultrasonography and magnetic resonance imaging of the parotid gland: can they replace the histopathologic studies in patients with Sjogren's syndrome? *Joint Bone Spine* 2004; 71: 29-38.
46. SALAFFI F, CAROTTI M, ARGALIA G, SALERA D, GIUSEPPETTI GM, GRASSI W: Usefulness of ultrasonography and color Doppler sonography in the diagnosis of major salivary gland diseases. *Reumatismo* 2006; 58: 138-56.
47. GIOVAGNORIO F, PACE F, GIORGI A: Sonography of lacrimal glands in Sjögren syndrome. *J Ultrasound Med* 2000; 19: 505-9.
48. REIMERS CD, FINKENSTAEDT M: Muscle imaging in inflammatory myopathies. *Curr Opin Rheumatol* 1997; 9: 475-85.
49. MENG C, ADLER R, PETERSON M, KAGEN L: Combined use of power Doppler and gray-scale sonography: a new technique for the assessment of inflammatory myopathy. *J Rheumatol* 2001; 28: 1271-82.
50. WEBER MA, JAPPE U, ESSIG M *et al*.: Contrast-enhanced ultrasound in dermatomyositis- and polymyositis. *J Neurol* 2006; 253: 1625-32.
51. KIM SH, KIM HO, JEONG YG *et al*.: The diagnostic accuracy of power Doppler ultrasonography for differentiating secondary from primary Raynaud's phenomenon in undifferentiated connective tissue disease. *Clin Rheumatol* 2008 Feb 2 [Epub ahead of print].